DEVELOPMENT OF SELECTIVE CARBON–CARBON BOND-FORMING REACTIONS OF VINYL CARBOCATIONS

Thesis by

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To my family

ACKNOWLEDGEMENTS

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way of teaching the subject made going to class something I actually enjoyed. Once I realized that organic chemistry was something that I was passionate about, Prof. Vadola invited me to join his research group, and those few years working in the lab really solidified my dream of pursuing a PhD in organic chemistry. I am very grateful to have learned so much from him; after all, he did teach nearly all of my organic chemistry courses. Outside of the classroom and lab, he always made time to chat with me about life; I appreciate all the advice that I received over those years, especially him preparing me for the fact that grad school is going to be hard (he was not wrong). Moreover, I also have to thank Profs. Caitlin Karver and Tim French for being a huge part of my support system during my time at DePaul. There were countless times where I would frantically email either of them, stressing out about something, and they would always find the time to meet with me. They provided so much support and advice, and I am very grateful for that.

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Last but not least, I think graduate school would have been a lot harder without my cats, Severus and Crookshanks. I couldn't have done it without them.

ABSTRACT

Carbocationic intermediates play an important role in the construction of complex molecules, from biosynthetic pathways in nature to the synthesis of natural products by organic chemists. In contrast to tricoordinated carbocations, dicoordinated vinyl carbocations have received less attention in the development of methods to form challenging carbon–carbon (C–C) bonds. However, the Nelson lab has recently disclosed a powerful catalytic platform for generating vinyl carbocations, which were then shown to proceed through carbon–hydrogen (C–H) insertion reactions to construct C–C bonds. This thesis further expands upon catalytic reactions of using vinyl carbocations to construct C–C bonds in a selective fashion.

To begin, a brief introduction that surveys C–C bond forming reactions of vinyl carbocations will be highlighted. These include seminal stoichiometric studies that have since been expanded to other catalytic systems. The discussion of experimental work outlined in this thesis commences with the development of a main group-catalyzed approach towards accessing α-vinylated esters through the trapping of vinyl carbocations with silyl ketene acetals to form sterically congested quaternary carbon centers fused to tetrasubstituted olefins. Next, a Claisen-type rearrangement will be discussed, which is a result of trapping vinyl carbocations with allyl ethers to form an allyl vinyl oxonium intermediate in situ that can subsequently undergo a [3,3] sigmatropic rearrangement. Finally, the last method that will be highlighted includes the development of an asymmetric C–H insertion reaction of vinyl carbocations to forge bicyclic products in a highly enantioselective fashion. Ultimately, this thesis work has expanded the scope of catalytic vinyl carbocation reactions that form C–C bonds selectively.

PUBLISHED CONTENT AND CONTRIBUTIONS

Portions of the work described herein were disclosed in the following publications:

1. Williams, C. G.; Nistanaki, S. K.; Wells, C. W.; Nelson, H. α-Vinylation of Ester Equivalents via Main Group Catalysis for the Construction of Quaternary Centers. *Org. Lett.* **2023**, *25*, 3591–3595. DOI: 10.1021/acs.orglett.3c00535, Copyright © 2023 American Chemical Society.

   C.G.W. participated in project design, conducted experiments, data acquisition and analysis, and writing of the manuscript.

2. Nistanaki, S. K.; Williams, C. G.; Wigman, B.; Wong, J. J.; Haas, B. C.; Popov, S.; Werth, J.; Sigman, M. S.; Houk, K.N.; Nelson, H. M. Catalytic asymmetric C–H insertion reactions of vinyl carbocations. *Science* **2022***, 378,* 1085–1091. DOI: 10.1126/science.ade5320, Copyright © 2022 American Association for the Advancement of Science.

   C.G.W. participated in project design, conducted experiments, data acquisition and analysis, and writing of the manuscript.

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LIST OF ABBREVIATIONS

α	alpha
Å	angstrom(s)
Ac	acetyl
acac	acetylacetonate
^{t}Am	*tert*-amyl
aq	aqueous
Ar, (het)Ar	generic aryl, heteroaryl group
β	beta
BINOL	1,1'-bi(2-naphthol)
BPin	pinacol boronic ester
Bn	benzyl
bp	boiling point
br	broad
Bu	butyl
^{13}C	carbon-13 isotope
ºC	degrees Celsius
ca.	about (Latin circa)
cat.	catalytic
cis	on the same side
cm^{-1}	wavenumber(s)
conc.	concentrated

Cy	cyclohexyl
CyH	cyclohexane
δ	delta
Δ	heat or difference
d	doublet
D	deuterium
dba	dibenzylideneacetone
dd	doublet of doublet
dt	doublet of triplet
ddd	doublet of doublet of doublet
DCE	1,2-dichloroethane
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
DTBP	di-*tert*-butyl peroxide
d.r.	diastereomeric ratio
E	trans (entgegen) olefin geometry
EDCI	*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
es	enantiospecificity
equiv	equivalents(s)

ESI	electrospray ionization
Et	ethyl
et. al.	and others (Latin: *et alii*)
EtOAc	ethyl acetate
FD	field desorption
γ	gamma
g	gram
GC-(FID)	gas chromatography (flame ionization detector)
gCOSY	gradient-selected correlation spectroscopy
^{1}H	proton
hr	hour(s)
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilazide
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectroscopy
HSQC	heteronuclear single quantum correlation
Hz	hertz
IDPi	imidodiphosphorimidate
i.e.	that is (Latin: *id est*)
i-Pr	isopropyl
in situ	in the reaction mixture
IPA	isopropanol, 2-propanol
IR	infrared (spectroscopy)

J	coupling constant
k	rate constant
K	Kelvin(s) (absolute temperature)
kcal	kilocalorie
L	liter
LA	Lewis acid
LDA	lithium diisopropylamide
μ	micro
m	multiplet; milli
m	meta
M	metal; molar; molecular ion
m/z	mass to charge ratio
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mol	mole(s)
MOM	methoxymethyl acetal
MS	molecular sieves or mass spectrometry
n-Bu	butyl
n-Pr	propyl
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy

Nu	nucleophile
o	ortho
o-DCB	1,2-dichlorobenzene
o-DFB	1,2-difluorobenzene
OTf	trifluoromethanesulfonate (triflate)
OTs	*p*-toluenesulfonate (tosylate)
p	para
PCC	pyridinium chlorochromate
Ph	phenyl
PMP	*p*-methoxyphenyl
ppm	parts per million
Pr	propyl
q	quartet
qd	quartet of doublets
R	generic for any atom or functional group
R_f	retention factor
Ref.	reference
rt	room temperature
s	singlet
sat.	saturated
SM	starting material
t	triplet
td	triplet of doublet

t-Bu	*tert*-butyl
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
temp.	temperature
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (trifyl)
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilyl
TOF	time-of-flight
Tol	tolyl
t_R	retention time
trans	on the opposite side
Ts	*p*-toluenesulfonyl (tosyl)
UV	ultraviolet
vide infra	see below
λ	wavelength
WCA	weakly coordinating anion
X	anionic ligand or halide
Z	cis (zusammen) olefin geometry

Chapter 1

Carbon–Carbon Bond-Forming Reactions via Vinyl Cation Intermediates

1.1 INTRODUCTION

Carbocations are enabling intermediates for the construction of carbon–carbon (C–C) bonds that have found broad utility in a variety of synthetic organic chemistry transformations.[1] In recent years, a subset of carbocations known as vinyl carbocations have shown their utility as powerful intermediates to forge C–C bonds.[2] However, compared to tricoordinated carbocations, vinyl cations and their reactivity have been less explored. The existence of vinyl cations was first suggested in the 1940s by Jacobs and Searles.[3] Since the initial discovery of vinyl cations, studies of these intermediates have been conducted by Rappaport, Grob, Hanack, Schleyer, and Stang, among others, to assess and further explore the reactivity of such intermediates.[4–12] This chapter will focus specifically on studies that involve vinyl cations in C–C bond-forming reactions. To that end, three general reactions of which C–C bonds are forged via vinyl cations will be highlighted: *1) rearrangements, 2) arylation reactions via Friedel–Crafts-type mechanism,*

and *3) C–H insertion reactions.*

Before discussing C–C bond-forming reactions of vinyl cations, it is important to first review common strategies for generating vinyl cation intermediates. The examples discussed in this chapter include forming vinyl cations through five general strategies: *1) ionization of vinyl leaving groups through solvolysis or Lewis acid abstraction, 2) decomposition of α-diazo-β-hydroxy carbonyls, 3) activation of alkynes through protonation, 4) activation of alkynes through electrophilic addition,* and *5) Lewis acid activation of alkynes.* As seen from these general strategies, common vinyl cation precursors that will be discussed in this chapter include those with ionizable vinyl groups, such as vinyl trifluoromethanesulfonates and vinyl(phenyl)iodonium salts. Additionally, vinyl cations are also commonly generated from alkynes through Brønsted or Lewis acid activation, as well as through addition of alkynes into electrophiles. Once the vinyl cation is generated, the reactive intermediate can proceed through one of the above mentioned C–C bond-forming reactions.

Relevant reports of forging C–C bonds with vinyl cations that do not fall under one of the mentioned categories will be discussed in the following chapters. The studies chosen for discussion in this chapter aim to highlight a range of methods, including both stoichiometric and catalytic approaches. Finally, reactions that have been developed as part of this thesis work will not be included in this chapter, as detailed discussions of these reactions will follow in Chapters 2–4.

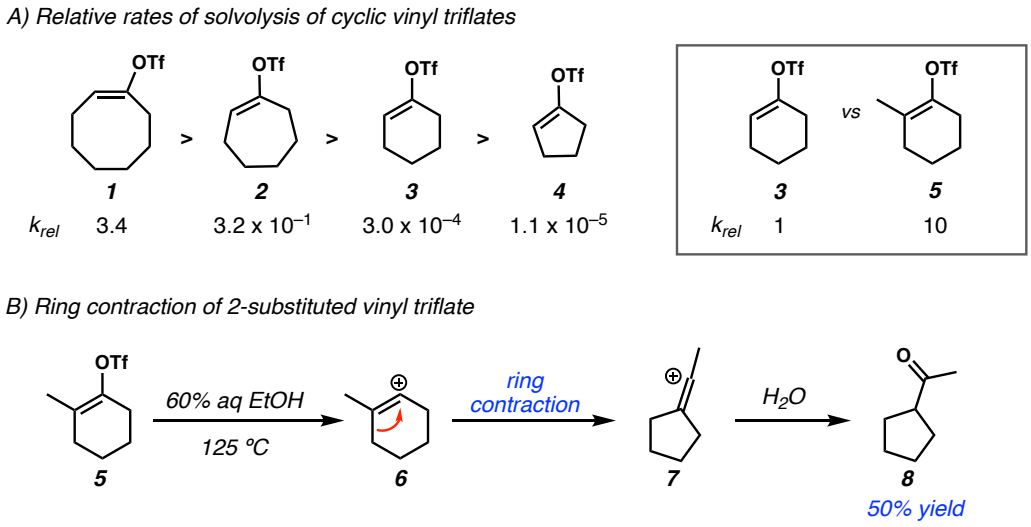
1.2 C–C BOND-FORMING REACTIONS

1.2.1 Rearrangements of Vinyl Cations

To begin, examples of vinyl cation intermediates undergoing rearrangements

including ring contraction and expansion events will be highlighted. Although some of these rearrangements involve subsequent steps that do not include C–C bond formation via vinyl cation intermediates, these studies are critical to understanding the reactivity and stability of these intermediates. As such, a discussion of these rearrangements is warranted in this chapter.

Scheme 1.1. *Schleyer, Hanack, Stang: solvolysis studies of cyclic vinyl triflates.*



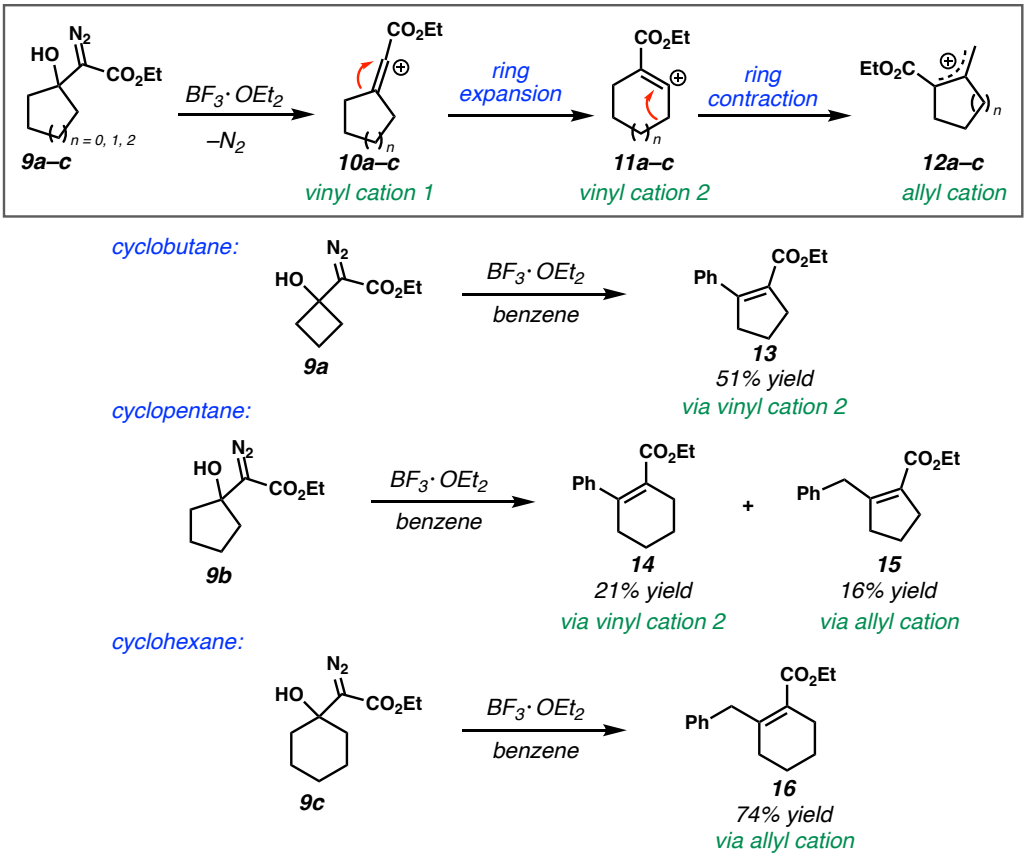
In the early 1970s, Schleyer, Hanack, and Stang disclosed a study measuring the rate of solvolysis of cyclic vinyl trifluoromethanesulfonates (triflates) in aqueous polar solvents at elevated temperatures, which resulted in the formation of vinyl cation intermediates.[13] Ketone products were observed as a result of water trapping the vinyl cation intermediates. Since vinyl cations are *sp*-hybridized, the relative rates of solvolysis for cyclic vinyl triflates **1**–**4** decrease with decreasing ring size, highlighting the instability of bent vinyl cations from vinyl triflates **3** and **4** (Scheme 1.1A). In this way, vinyl cations are analogous to cyclic alkynes, where accessing smaller than 8-membered cyclic alkynes results in only

transient and unstable intermediates.[14] However, it was found that vicinal alkyl substituents can enhance the rate of solvolysis 10-fold, as seen with vinyl triflate **3** vs **5**. By subjecting vinyl triflate **5** to the reaction conditions, the expected substituted cyclohexanone product was not observed, and instead, cyclopentanone **8** was obtained in 50% yield (Scheme 1.1B). The authors rationalized this as the initial cyclic vinyl cation **6** undergoing a ring contraction via an alkyl migration to generate the comparably more stable linear vinyl cation **7**, which is subsequently trapped with water to produce **8**. This ring contraction is not possible with vinyl triflate **3**, as a monosubstituted vinyl cation would be formed. While the rearrangement results in the formation of another vinyl cation intermediate that is subsequently quenched by solvent, this report ultimately represents one of the earliest reported examples of vinyl cations forming a C–C bond.

Next, Pellicciari and coworkers investigated rearrangements of destabilized vinyl cations generated by treating α-diazo-β-hydroxy esters (**9a–c**) with boron trifluoride etherate (Scheme 1.2).[15] Due to the instability of the vinyl cation as a result of being adjacent to an electron-withdrawing ester, vinyl cation 1 (**10a–c**) undergoes ring expansion via a 1,2-alkyl shift to form the more stable intermediate, vinyl cation 2 (**11a–c**). Another ring contraction can lead to the allyl cation (**12a–c**), which is then trapped by benzene solvent via Friedel–Crafts-type mechanism. The authors noted that for cyclobutane α-diazo-β-hydroxy ester **9a**, cyclopentene **13** was obtained in 51% yield. This suggested that the second ring contraction rearrangement (**11a** to **12a**) did not proceed, which was likely a result of a high energy barrier for rearrangement of **11a** due to the ring strain of the cyclobutenyl allyl cation intermediate **12a**. However, for the 5-membered α-diazo-β-hydroxy ester (**9b**), a mixture of products (**14** and **15**) was observed as a result of trapping both **11b** and **12b**. The authors suggested that

this is perhaps a result of a high barrier to the allyl cation intermediate, ultimately resulting in an unselective mixture of products. In contrast, for the 6-membered α-diazo-β-hydroxy ester analog (**9c**), the major product (**16**) was obtained in 74% yield, which was a result of trapping the allyl cation **12c** after both ring expansion of **10c** followed by ring contraction of **11c**.

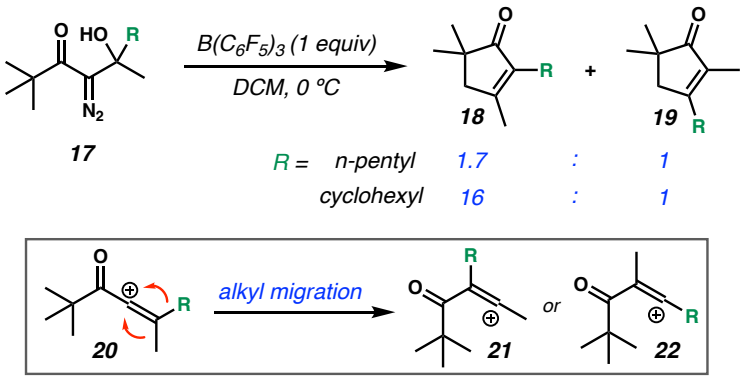
Scheme 1.2. *Pellicciari: rearrangements of destabilized vinyl cations.*



More recently, Brewer and coworkers disclosed a study measuring the migratory aptitude of similarly destabilized vinyl cation intermediates, generated through the decomposition of α-diazo-β-hydroxy ketones (**17**) by the Lewis acid $B(C_6F_5)_3$, that gave rise

to products **18** and **19** (Scheme 1.3).[16,17] They demonstrated that once vinyl cation **20** is formed, alkyl migration can lead to either intermediates **21** or **22**, but migration of the more electron-rich group was favored. For example, migration of an *n*-pentyl substituent was slightly favored over methyl migration, resulting in a 1.7:1 ratio between products **18** and **19**, which were formed from intramolecular C–H insertion of vinyl cation intermediates **21** and **22** into the methyl C–H bond of the *t*-butyl substituent. Moreover, a secondary cyclohexyl substituent was favored over the methyl, now in a 16:1 ratio.

Scheme 1.3. *Brewer: migratory aptitude of alkyl substituents.*



These examples by Schleyer, Pellicciari, and Brewer highlight the ability of vinyl cations to undergo C–C bond-forming rearrangements, which is ultimately driven by the formation of more stable vinyl cation intermediates. The resulting more stabilized vinyl cation is then trapped with solvent or proceeds through intramolecular C–H insertion.

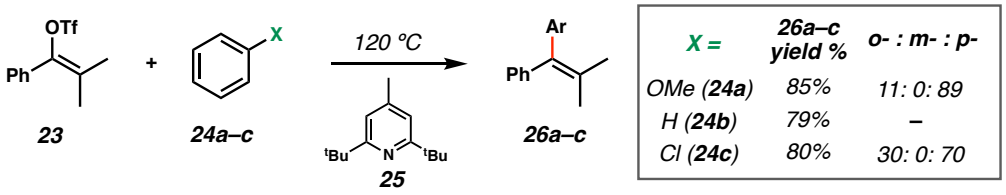
1.2.2 Friedel–Crafts Reactivity

Similar to tricoordinate carbocations, vinyl cations are also known to undergo reactions with arenes via a Friedel–Crafts mechanism. Since the early 1970s, various methods,

including catalytic protocols, have been developed to harness vinyl cations and their reactions with arenes, both in an inter- and intramolecular fashion. This section of the chapter discusses some of these reports.

As previously discussed, early studies of vinyl cations involved solvolysis of vinyl triflates in aqueous polar solvents, which resulted in the trapping of vinyl cation intermediates with solvent or water to generate ketone products.[13] In the late 1970s, Stang disclosed that cyclic and acyclic vinyl triflates could also be solvolyzed in arene solvents at elevated temperatures, which ultimately furnished products that resulted from trapping of the cation with the arene solvent via a Friedel–Crafts mechanism.[18,19] These results represent some of the earliest examples of forming C–C bonds via vinyl cation intermediates in an intermolecular fashion. For example, by subjecting vinyl triflate **23** to various arenes (**24a–c**) in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (**25**) at 120 ºC, arylated products **26a–c** were accessed in good yields (Scheme 1.4). Products **26a** and **26b** were formed in 85% and 79% yield, respectively, from Friedel–Crafts with anisole (**24a**) and benzene (**24b**). In addition, product **26c**, resulting from Friedel–Crafts with electron-poor chlorobenzene **24c**, was also furnished in 80% yield. The selectivity for the arylated products resulted from favoring alkylation at the activated positions of the arene. To note, a non-nucleophilic base, 2,6-di-*tert*-butyl-4-methylpyridine **(25**), was added to quench the acid generated from the Friedel–Crafts reaction.

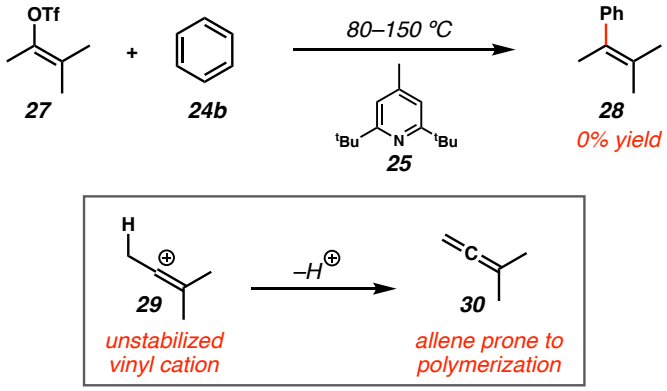
Scheme 1.4. *Stang: solvolysis of vinyl triflate in arene solvent.*



X =	26a–c yield %	o- : m- : p-
OMe (**24a**)	85%	11: 0: 89
H (**24b**)	79%	–
Cl (**24c**)	80%	30: 0: 70

If the resulting vinyl cation could make a stable allene or alkyne product via E_1-type pathways, arylation was not observed. For example, trimethyl vinyl triflate **27** led to no formation of arylated product **28** (Scheme 1.5). Instead, it yielded what the authors described as a tar-like material as a result of facile deprotonation of the vinyl cation intermediate (**29**) to form the corresponding allene (**30**) that readily underwent polymerization at elevated temperatures.

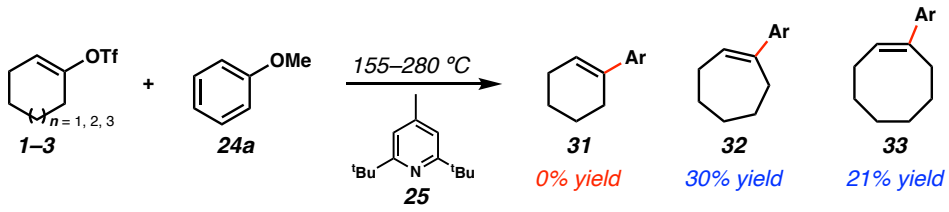
Scheme 1.5. *Stang: trialkyl vinyl triflate fails to undergo arylation reaction.*



The rates of solvolysis in polar media that were previously discussed for cyclic vinyl triflates (Scheme 1.1)[13] are also consistent for solvolysis in arene solvent. For example, 7- and 8-membered cyclic vinyl triflates (**1** and **2**) yielded products **32** and **33**, but the 6-

membered variant (**3**) did not furnish **31** (Scheme 1.6). This is likely due to the high energy of the intermediate as a result of the strained ring system. As previously mentioned, the solvolysis of 6-membered vinyl triflate **3** in aqueous polar ethanol was 10^4 times slower than the 7-membered variant (**2**).

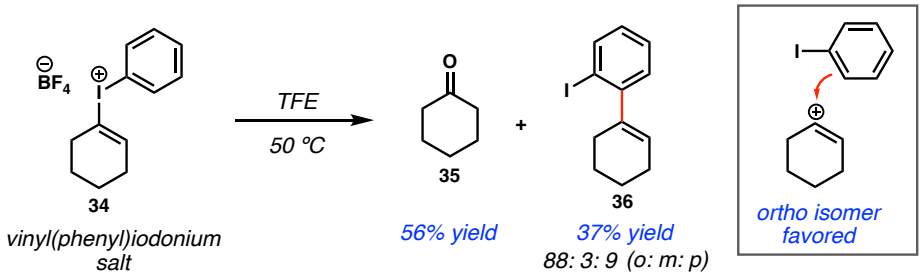
Scheme 1.6. *Stang: solvolysis of cyclic vinyl triflates in anisole.*



Up until this point in the chapter, much of the solvolysis studies discussed have been focused on generating vinyl cations from vinyl triflates. However, Okuyama and coworkers have demonstrated that vinyl cations can also be generated through solvolysis of vinyl iodonium salts under milder conditions (Scheme 1.7).[20] For example, by subjecting phenyl vinyl iodonium **34** to aqueous alcohol solvent at temperatures between 25–50 ºC, products **35** and **36** were formed. Similar to the previously discussed solvolysis reactions, cyclohexanone **35** was produced as a result of alcohol or water solvent trapping the resulting vinyl cation, followed by hydrolysis upon workup. Yields were rather low when the reaction was performed in ethanol or methanol solvent, but by moving to trifluoroethanol, **36** was observed in 37% yield, where the *ortho* isomer was largely favored compared to the *meta* or *para* isomers. This observed selectivity contrasts with traditional Friedel–Crafts reactions where the *para* isomer is typically the major product.[18,19] The authors attributed this product ratio to an intimate ion pair between the vinyl cation intermediate and the iodoarene after

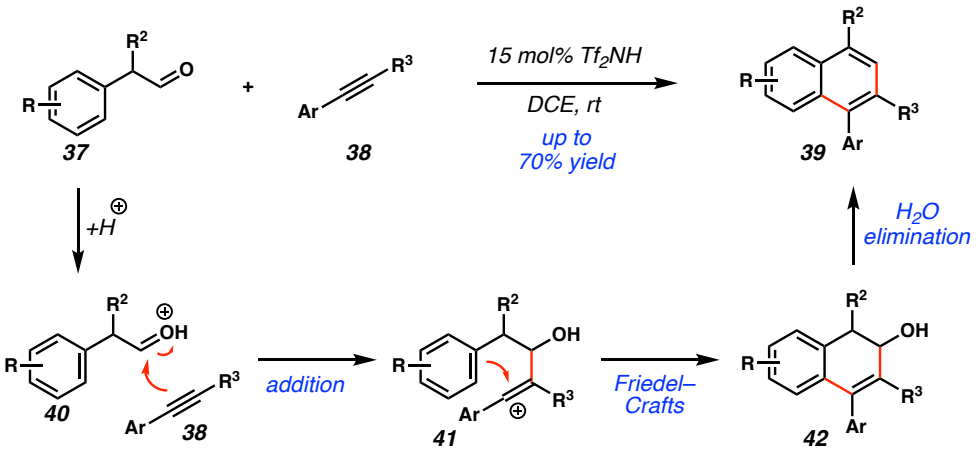
ionization, where the orientation of the arene was largely retained. If the arene and the vinyl cation did dissociate, then the traditional Friedel–Crafts product ratio would be expected, favoring the *para* isomer.

Scheme 1.7. *Okuyama: vinyl(phenyl)iodonium salts as vinyl cations precursors for arylation reaction.*



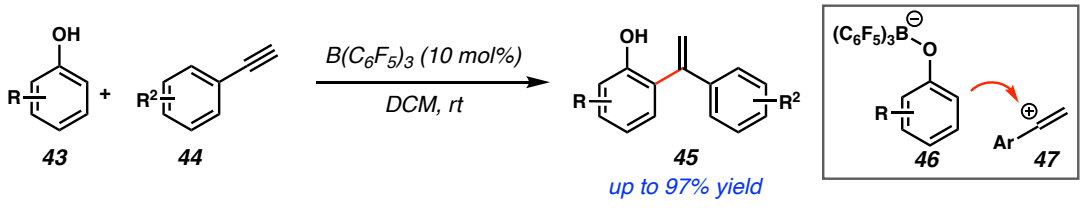
Next, acid-catalyzed Friedel–Crafts reactions of vinyl cations generated from alkynes will be discussed. Ponra and coworkers have reported a Brønsted acid-catalyzed reaction to access substituted naphthalene products (**39**) through the coupling of aldehydes (**37**) with alkynes (**38**) (Scheme 1.8).[21] This intermolecular reaction first involves activation of an aldehyde through protonation by the Brønsted acidic Tf_2NH, and then the alkyne (**38**) coupling partner adds into the activated oxocarbenium (**40**), furnishing vinyl cation **41**. The resulting vinyl cation (**41**) is then poised to undergo an intramolecular Friedel-Crafts reaction to form the fused-ring core (**42**). Dehydration of the alcohol results in product formation (**39**) and generation of the Brønsted acid catalyst. These mild reaction conditions allow for the formation of a variety of substituted naphthalene products in good yield.

Scheme 1.8. *Ponra: acid-catalyzed intermolecular coupling of aldehydes and alkynes.*



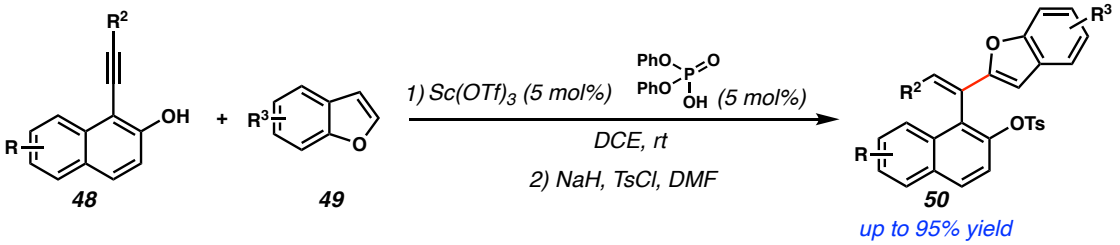
Li and coworkers disclosed a catalytic Lewis acid strategy to couple phenols (**43**) with phenyl acetylenes (**44**) in an intermolecular fashion via Friedel–Crafts to access diaryl substituted alkenes (**45**) (Scheme 1.9).[22] First, the proposed mechanism begins with Lewis acid activation of the phenol (**43**) to generate (**46**), which results in a proton transfer to the alkyne to generate the vinyl cation intermediate (**47**). The phenyl borate species (**46**) acts as the counter anion to the vinyl cation, forming an ion pair. Then, an *ortho* selective Friedel–Crafts reaction occurs to generate diaryl substituted alkenes. The authors attributed the *ortho* selectivity towards the ion pair of the phenyl borate with the vinyl cation, but further mechanistic evidence was not provided.

Scheme 1.9. *Li: Lewis acid-catalyzed coupling of phenols and alkynes.*



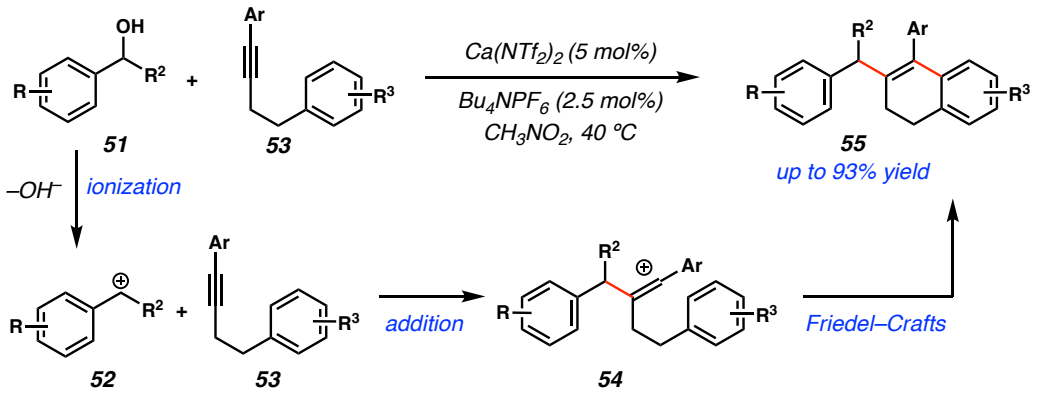
Another Lewis acid-catalyzed approach towards coupling alkynes (**48**) with arenes (**49**) in an intermolecular fashion to access di- and triaryl products (**50**) was reported by Sun and coworkers (Scheme 1.10).[23] Here, the proposed mechanism begins with the activation of alkynes with a $Sc(OTf)_3$ Lewis acid that is paired with a phosphoric acid to generate vinyl cations that can proceed through intermolecular Friedel–Crafts with heteroarenes, like benzofuran. It is important to note that without the Lewis acid, products resulting from [4 + 2] cycloadditions were obtained instead, highlighting the necessity of Lewis acid activation of the alkyne to form the vinyl cation intermediate.

Scheme 1.10. *Sun: Lewis acid-catalyzed coupling of alkynes with heteroarenes.*



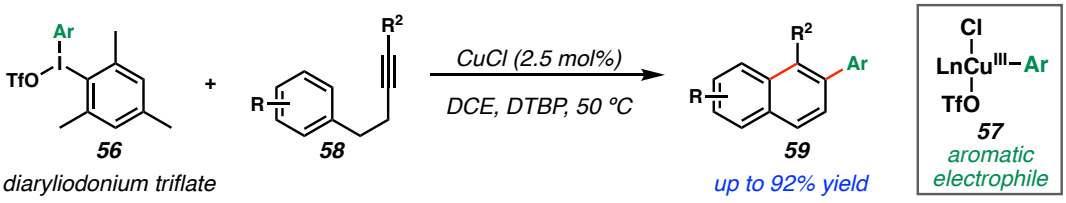
A similar intramolecular carboarylation of alkynes has also been reported by Niggemann and coworkers using a Lewis acidic $Ca(NTf_2)_2$ catalyst (Scheme 1.11).[24] The proposed mechanism begins with the loss of hydroxide from phenylethanol **51** by the catalyst to form a benzylic secondary carbocation **52**. The alkyne coupling partner (**53**) then adds into the electrophilic carbocation intermediate. This addition results in the formation of a vinyl cation (**54**), which can then proceed through intramolecular Friedel–Crafts to form the observed product (**55**). The authors demonstrated this reaction on a variety of substituted coupling partners.

Scheme 1.11. *Niggemann: carboarylation of alkynes.*



Gaunt and coworkers have also developed copper-catalyzed alkyne carboarylation reactions (Scheme 1.12).[25] Here, an aromatic electrophile is generated through activation of diaryliodonium salt **56** with catalytic CuCl to form Cu species **57**. The alkyne partner (**58**) then reacts with the electrophilic arene. The resulting vinyl cation proceeds through intramolecular Friedel–Crafts to form the substituted naphthalene products (**59**) in good yield.

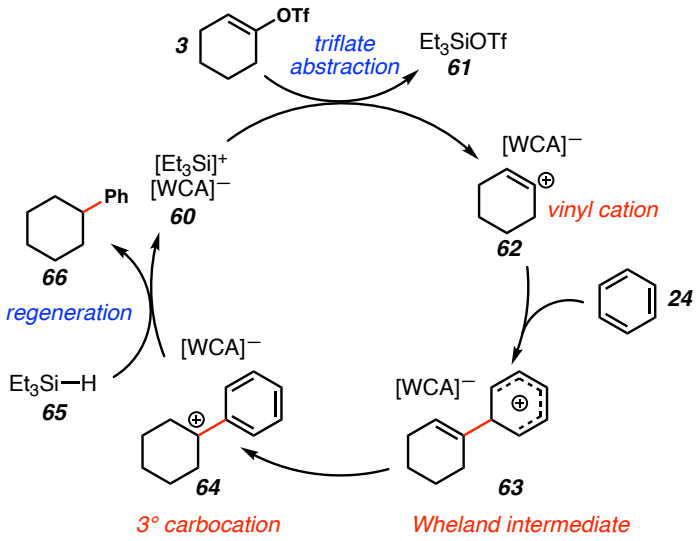
Scheme 1.12. *Gaunt: alkyne addition to Cu–aryl electrophile and cyclization.*



In 2018, Nelson and coworkers disclosed that vinyl cations could be generated through the ionization of vinyl triflates using catalytic quantities of a Lewis acid in nonpolar solvents. Herein, a Lewis acidic silylium species paired with a weakly coordinating *mono*-carborane

anion (**60**) abstracts a triflate from vinyl triflate **3** to generate Et_3SiOTf (**61**) and the resulting vinyl cation (**62**) (Scheme 1.13).[26] Due to the hyper Lewis acidity of the silylium species, even strained cyclic vinyl cations could be generated. Once the vinyl cation is formed, it can react with an arene to form a cationic Wheland intermediate (**63**). Tautomerization leads to tertiary carbocation **64**, and finally reduction of the cation by stoichiometric Et_3SiH (**65**) furnishes the final product (**66**) and regenerates the silylium species. The key to this reactivity is the use of the WCA. After ionization of the vinyl triflate, the vinyl cation intermediate is paired with this non-basic and non-nucleophilic anion. This anion does not quench the cation via elimination or substitution, ultimately allowing for the reactive vinyl cation to react with arenes as well as aliphatic hydrocarbons, which will be discussed in section 1.2.3.

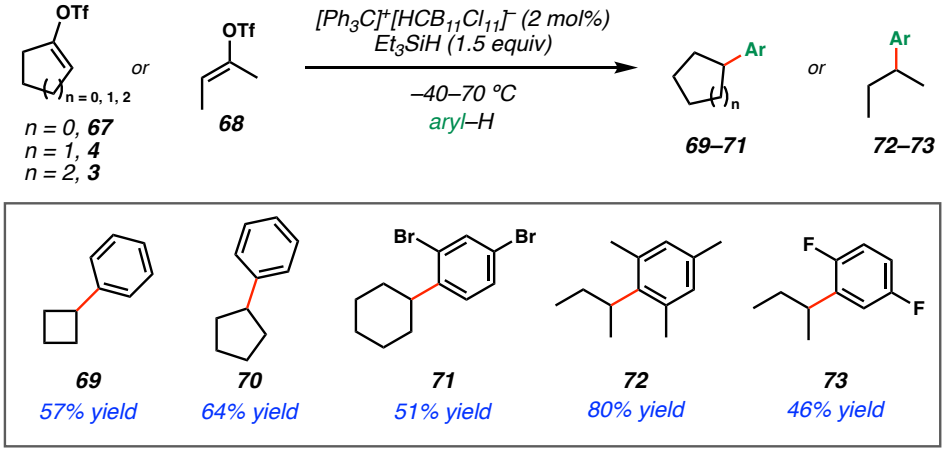
Scheme 1.13. *Nelson: catalytic cycle for reductive arylation of vinyl triflates.*



As shown, products **69**–**73** can be generated from strained, cyclic vinyl triflates (**3**, **4** and **67**), as well as acyclic vinyl triflate **68** (Scheme 1.14).[26] This is in contrast to the

previously discussed solvolysis reaction of vinyl triflates, which were unsuccessful in obtaining the desired arylated products using cyclic triflates with less than 7 carbons.[18,19] Similarly, in previous studies by Stang, trialkyl vinyl triflates did not afford the desired reactivity (Scheme 1.5).

Scheme 1.14. *Nelson: examples of products accessed via reductive arylation.*



In summary, various Friedel–Crafts reactions of vinyl cations have been discussed. These include stoichiometric solvolysis reactions, as well as methods that have been developed to generate vinyl cations from alkynes. Lastly, recent work by Nelson and coworkers was briefly discussed, which utilizes a Lewis acidic silylium species to abstract a triflate, resulting in the formation of a reactive vinyl cation that can react with arenes via a Friedel–Crafts mechanism.

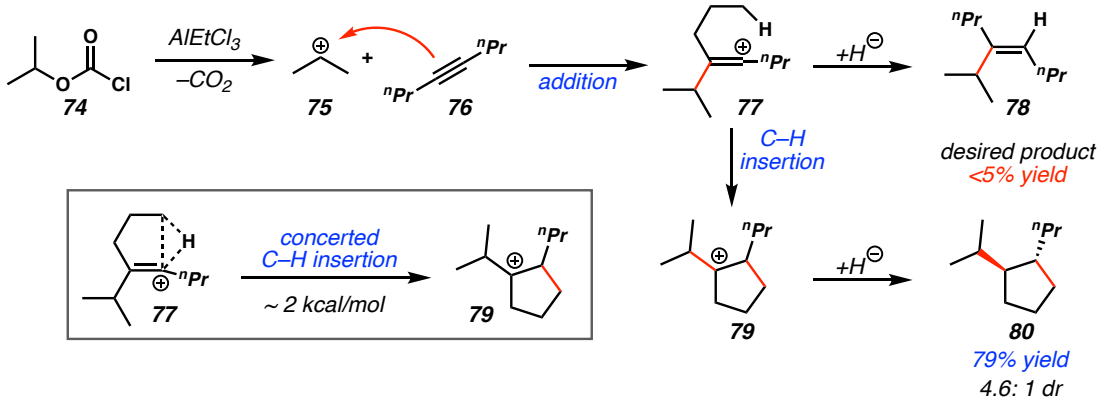
1.2.3 C–H Insertion Reactions of Vinyl Cations

In addition to Friedel–Crafts reactions, vinyl cations have also been demonstrated to undergo insertion reactions into C–H bonds, either in a stepwise or concerted fashion. This

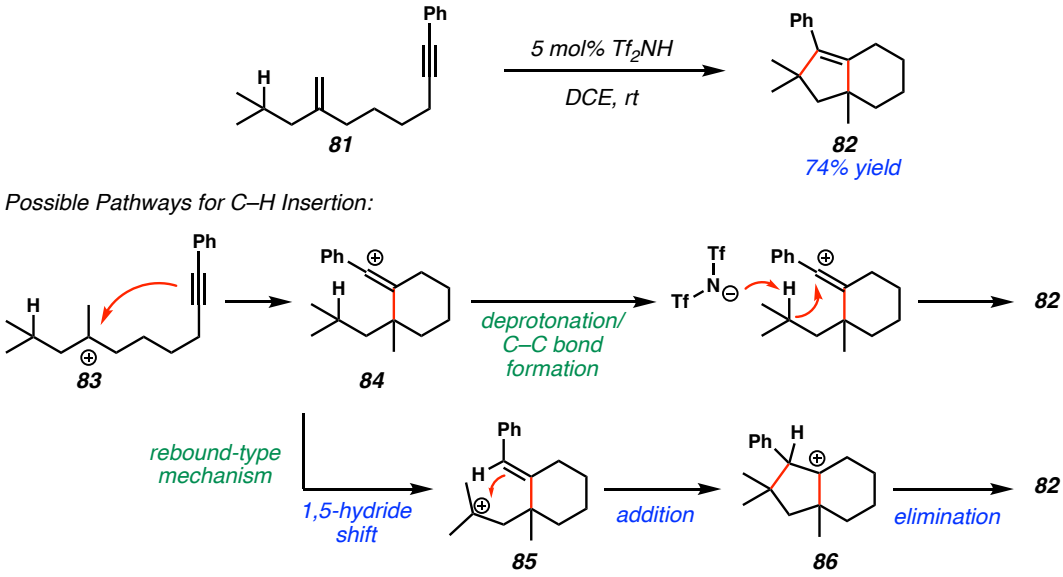
section of this chapter discusses current reports of such reactivity.

One of the early examples of C–H insertion of vinyl cations was reported by Metzger and coworkers. Prior to this work, they had reported a hydroalkylation reaction, where the addition of $Et_3Al_2Cl_3$ to alkyl chloroformate **74** generated isopropyl cation **75**, which can then add across alkenes and be subsequently reduced to the alkane product.[27] They expected that by moving from alkenes to alkynes (**76**), vinyl cation **77** would allow access to the analogous hydroalkylation product (**78**). However, by expanding the system from alkenes to alkynes in the presence of $SiEt_3H$, cyclopentane product **80** was isolated with little formation of the desired hydroalkylation product **78** (Scheme 1.15).[28] The authors proposed that once the isopropyl cation **76** adds to the alkyne and vinyl cation **77** is formed, a concerted C–H insertion proceeds to form intermediate **79**, as the activation energy for a concerted process was approximately 1.9 kcal/mol. After C–H insertion, the resulting tertiary carbocation **79** was subsequently reduced. The cyclopentane product **80** was accessed in 79% yield as a 4.6:1 mixture of diastereomers.

Scheme 1.15. *Metzger: concerted C–H insertion of vinyl cations.*



Scheme 1.16. *Yamamoto: Brønsted acid-catalyzed cyclization reaction.*

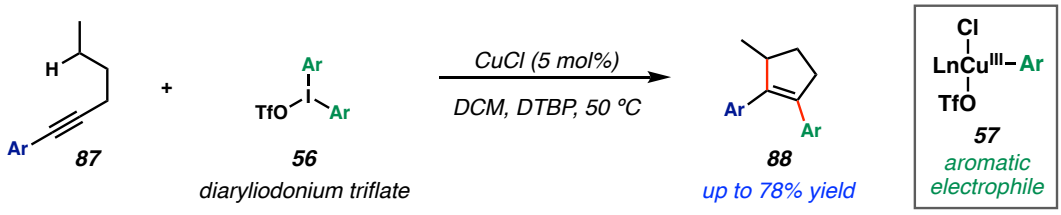


It was not until decades after the initial discovery of vinyl cations that catalytic platforms involving these intermediates were developed to construct C–C bonds. One of the early examples was disclosed by Yamamoto in a Brønsted acid-catalyzed cyclization reaction of cyclic and acyclic enynes (**81**) to form bicyclic products (**82**) (Scheme 1.16).[29] The proposed reaction begins with the protonation of an alkene from catalytic TfOH or Tf_2NH to form intermediate **83**. Then, the attack of the tertiary carbocation by the alkyne proceeds, which forms vinyl cation **84**. From vinyl cation **84**, two mechanistic pathways are proposed. The authors suggest that the C–H bond of the terminal isopropyl fragment is activated by the Brønsted counter anion, which is key to a concerted deprotonation and C–C bond-forming pathway to form the kinetically-favored 5-membered ring. Moreover, this also regenerates the Brønsted acid catalyst. However, the authors do not rule out an alternative, rebound-type mechanism. Upon the formation of vinyl cation **84**, a 1,5-hydride shift can occur, forming tertiary carbocation **85**. The addition of the alkene to the carbocation can then

proceed, and through the elimination of intermediate **86**, (**82**) is formed. Mechanistic investigation of these two pathways was not disclosed. This report represents the first example of a C–H activation of an unactivated C(sp^3)–H bond via Brønsted acid catalysis.

As discussed in section 1.2.2, Gaunt and coworkers have developed an alkyne carboarylation reaction, utilizing diaryliodonium salts (**56**) and catalytic CuCl to generate an electrophilic aromatic reagent (**57**) that can react with alkynes (Scheme 1.12).[25] They have further expanded this system to generate substituted cyclopentene products via C–H insertion of vinyl cations. Similarly, addition to phenyl acetylenes (**87**) forms the substituted vinyl cation intermediate. The cation reacts with the appended alkyl chain via C–H insertion to furnish the cyclopentene products (**88**) in up to 78% yield (Scheme 1.17).[30]

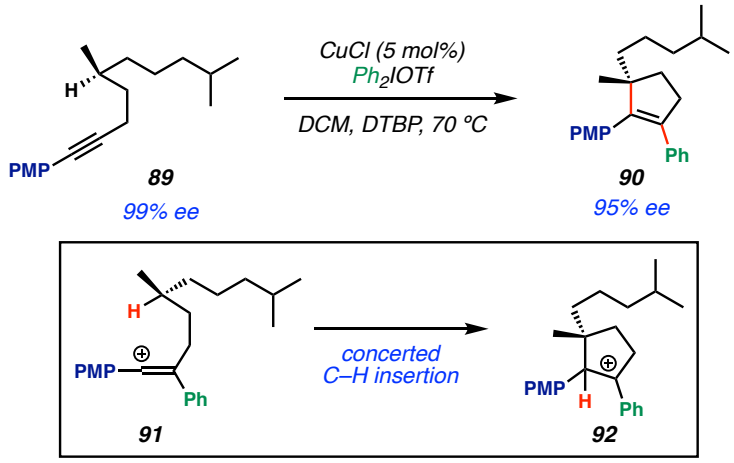
Scheme 1.17. *Gaunt: alkyne cyclization cascade to furnish cyclopentenes.*



To probe the C–H insertion mechanism, enantioenriched alkyne **89** was prepared and subjected to the reaction conditions (Scheme 1.18). The desired cyclopentene product **90** was obtained with 95% ee. With this result, the authors suggested that a concerted C–H insertion was proceeding, similarly to the proposed pathway described by Metzger and coworkers. If a rebound-type pathway was operative, a 1,5-hydride shift would have destroyed the stereocenter by forming a tertiary carbocation. Since this was not the case, a

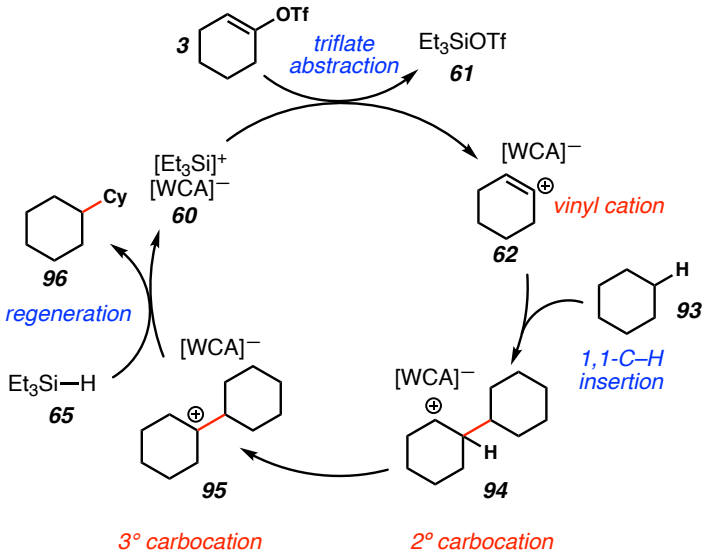
concerted C–H insertion of vinyl cation intermediate **91** is likely operative to form the C–C bond in intermediate **92**, which is subsequently deprotonated to **90.**

Scheme 1.18. *Gaunt: enantioenriched alkyne cyclization study.*

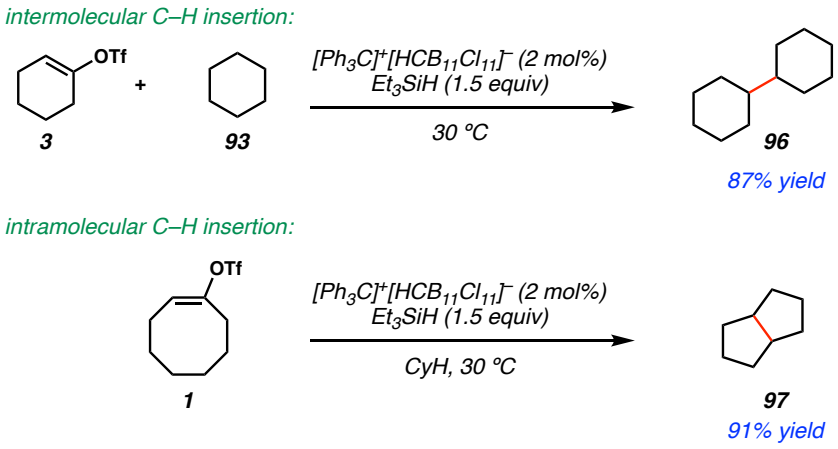


As previously mentioned in section 1.2.2, in 2018, Nelson and coworkers disclosed that vinyl cations could be generated through the ionization of vinyl triflates by a Lewis acidic silylium species paired with a WCA.[26] In addition to the discussed Friedel–Crafts reactivity, Nelson and coworkers also demonstrated that the vinyl cation intermediates can react with unactivated C(sp^3)–H bonds of hydrocarbons (Scheme 1.19). After the vinyl cation **62** is formed, a 1,1-C–H insertion event with hydrocarbons, like cyclohexane (**93**), can occur to furnish a secondary cation intermediate (**94**). A hydride shift can then proceed to form the more stable tertiary cation (**95**), which is then reduced by Et_3SiH (**65**) to form the final product (**96**) and regenerate the active Lewis acid catalyst.

Scheme 1.19 *Nelson: catalytic cycle for hydrocarbon C–H insertion reactions.*



Scheme 1.20. *Nelson: examples of C–H insertion reactions.*

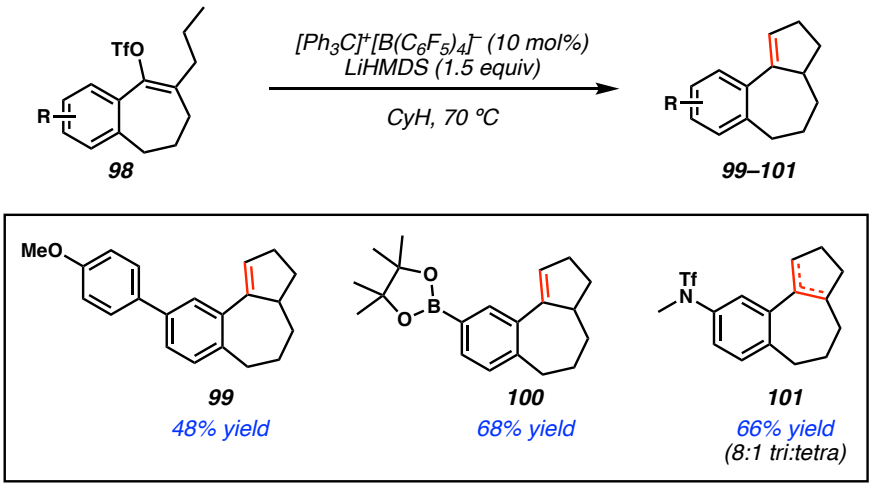


As shown in Scheme 1.20, C–H insertion of cyclohexane forms bicyclohexyl **96** in 87% yield at room temperature. Additionally, intramolecular transannular C–H insertions can also be performed. Cyclooctenyl vinyl triflate **1** yielded bicyclo[3.3.0]octane **97** in 91% yield.[26] These results demonstrate a powerful approach towards C–H functionalization of

hydrocarbon molecules by utilizing reactive vinyl cation intermediates, which can react with inert C(sp^3)–H bonds at room temperature.

Nelson and coworkers later disclosed milder Lewis acidic lithium conditions (as compared to silylium conditions) for generating vinyl cations that could then undergo C–H insertion reactions in an intramolecular fashion. Here, a lithium Lewis acid paired with a WCA was still a competent Lewis acid for the ionization of vinyl triflates (**98**) (Scheme 1.21).[31] In contrast to the silylium conditions, olefinic products (**99–101**) were obtained. Stoichiometric LiHMDS was required to turn over the catalytic system by deprotonation of the cationic intermediate after C–H insertion. Moreover, heteroatom moieties, like methoxy groups, boronates, and triflamides, were tolerated under these milder conditions, allowing access to products **99–101**.

Scheme 1.21. *Nelson: C–H insertion reactions of vinyl cations generated under basic conditions.*



This section of Chapter 1 discusses C–C bond-forming reactions of vinyl cations that proceed through C–H insertion reactions. Compared to Friedel–Crafts reactivity, fewer methods have been developed to take advantage of this powerful approach towards forging C–C bonds through C–H insertion reactions.

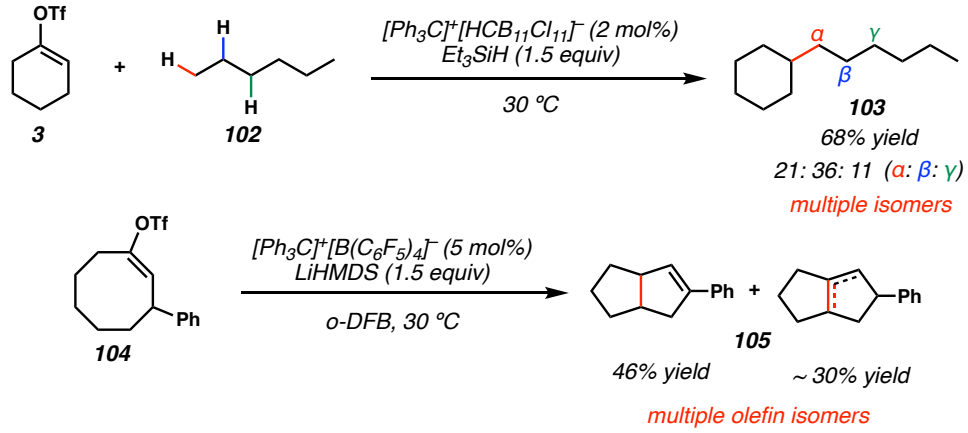
1.3 CONCLUDING REMARKS

In conclusion, vinyl cations are powerful intermediates for the construction of C–C bonds. Since the early studies by Schleyer, Hanack, and Stang, a variety of methods have been developed to construct various carbocyclic frameworks via these intermediates. This chapter first discussed examples of vinyl cations undergoing alkyl migrations. The rearrangements of vinyl cations are driven by the formation of more stable vinyl cation intermediates, and this is largely demonstrated for strained, cyclic vinyl cations. The next section of this chapter portrays both stoichiometric and catalytic methods that involve vinyl cations proceeding through Friedel–Crafts reactions. This reactivity was first demonstrated by Stang in the 1970s through the solvolysis of vinyl triflates in arene solvent, and then later by Okuyama and coworkers through the solvolysis of vinyl(phenyl)iodonium salts. More recently, methods have been developed utilizing Brønsted and Lewis acid catalysts for coupling alkynes with arenes, both in an inter- and intramolecular fashion. However, it was not until the recent work by Nelson and coworkers that vinyl cations could be generated in a catalytic fashion through triflate abstraction from a Lewis acid catalyst, which stands in contrast to the solvolysis studies as well as vinyl cation formation from alkyne precursors. Through their developed catalytic platform, vinyl cations were observed to undergo arylation reactions readily, including strained, cyclic vinyl triflates that were previously challenging substrates in solvolysis studies. Lastly, the third and final

component of this chapter was a brief discussion of C–H insertion reactions of vinyl cations. Up until recently, the majority of the reports were limited to generating vinyl cations from alkyne starting materials for subsequent C–H insertion reactions. Now with the developed catalytic methods by Nelson and coworkers, vinyl cations can be generated from simple vinyl sulfonates derived from ketones that can engage in C–H insertion reactions to form C–C bonds.

Despite these advantages of the catalytic platforms developed by Nelson and coworkers, challenges still exist with these methodologies (Scheme 1.22). For example, in intermolecular reactions using alkanes with more than one site for C–H insertion, multiple isomers are generated. This is seen in the case of *n*-hexane (**102**), where product **103** is formed as a mixture of isomers. Moreover, transannular C–H insertion from vinyl triflate **104** also yields an unselective mixture of olefinic products **105** due to unselective deprotonation under the lithium/basic conditions.

Scheme 1.22. *Current challenges in C–H insertion reactions of vinyl cations.*



These challenges presented an opportunity for further advancement of selective reactions. Thus, my PhD studies focused on developing selective C–C bond-forming reactions utilizing vinyl carbocation intermediates. First, this has been demonstrated through the optimization of a reaction platform that traps vinyl carbocations with carbon-centered nucleophiles to form sterically congested quaternary carbon centers. The second method that has been investigated is a sigmatropic rearrangement that relies on trapping vinyl carbocations with allyl ethers to generate a cationic intermediate that can subsequently rearrange, resulting in selective C–C bond formation. The third method developed is an enantioselective C–H insertion reaction. This method accesses products in a highly selective fashion, in terms of enantioselectivity, diastereoselectivity, and olefin isomer selectivity. The following chapters will discuss these reactions in detail.

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Chapter 2

α–Vinylation of Ester Equivalents via Main Group Catalysis for the Construction of Quaternary Centers[†]

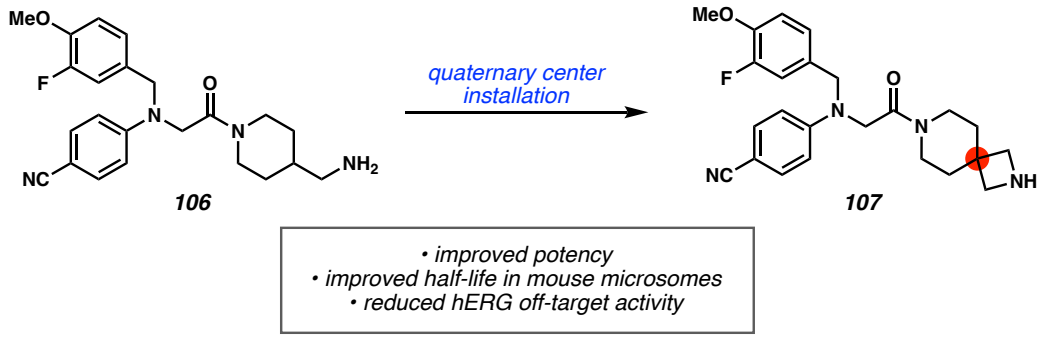
2.1 INTRODUCTION

All-carbon quaternary centers are critical structural motifs found in various natural products and pharmaceutical drug molecules.[1] Along with increasing the structural complexity of molecules, these moieties have been shown to enhance the potency, selectivity, and metabolic stability of bioactive compounds targeted in drug discovery campaigns.[1e] For example, Mould and coworkers showed in the development of reversible inhibitors for lysine specific demethylase 1 (LSD1), a histone that plays a role in cancers such as leukemia, that the introduction of a quaternary center to **106** to afford **107** more

[†] Portions of this chapter have been adapted from Williams, C. G.; Nistanaki, S. K.; Wells, C. W.; Nelson, H. M. α-Vinylation of Ester Equivalents via Main Group Catalysis for the Construction of Quaternary Centers. *Org. Lett.* **2023**, *25,* 3591–3595. DOI: 10.1021/acs.orglett.3c00535.

than doubled the molecule's potency towards its target, increased its half-life in mouse microsomes, and improved hERG inhibition liability (Scheme 2.1).[2]

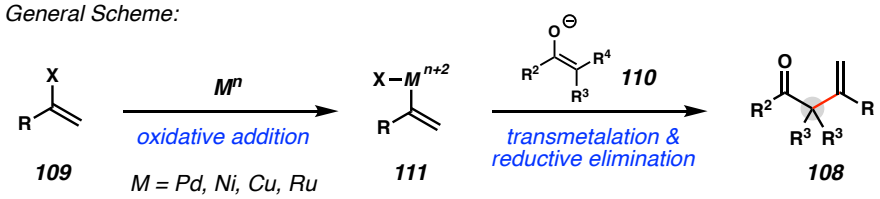
Scheme 2.1. *Enhanced pharmacokinetics through installation of quaternary center.*



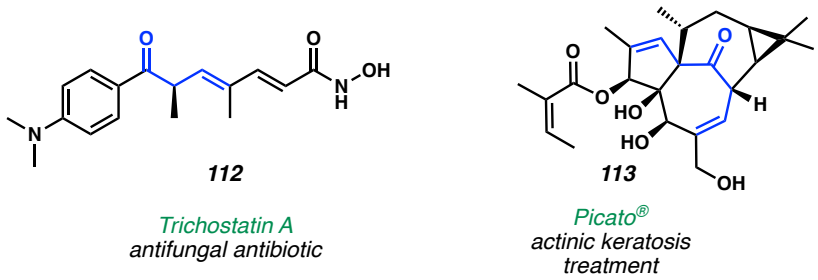
Despite these clear advantageous effects, the construction of quaternary centers is still a challenging synthetic problem due to the high steric environment they contain.[3] While enolate alkylation is a known strategy towards accessing quaternary centers, this approach is typically limited to the construction of C(sp^3)–C(sp^3) bonds, with few examples of Michael-type additions of 1,3-dicarbonyl compounds into activated alkynes reported.[4] Moreover, various transition metal-catalyzed methodologies have been developed to form C(sp^3)–C(sp^2) bonds to access products of type **108** through cross-coupling of aryl and alkenyl electrophiles (**109**) with enolate equivalents (**110**) (Scheme 2.2).[5] Many of these include α-vinylation or α-arylation of ketone enolates or their derivatives using transition metals, such as palladium, nickel, copper, or ruthenium.[6] In particular, α-vinylation of enolate equivalents is a powerful approach towards accessing β,γ-unsaturated carbonyl

motifs, which are prevalent in bioactive natural products and medicines (**112** and **113**, Scheme 2.3).[7]

Scheme 2.2. *Transition metal-catalyzed α-vinylation of enolates.*



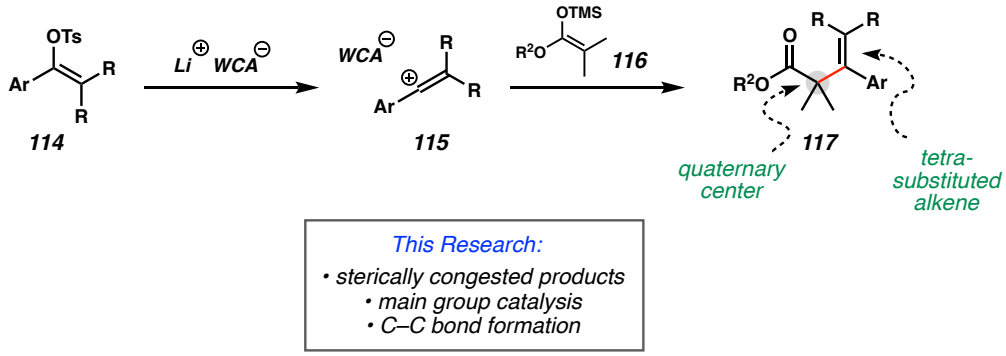
Scheme 2.3. *Examples of bioactive molecules with α-vinylated carbonyl motifs.*



While useful, two drawbacks of current catalytic α-vinylation methods exist: (1) the requirement of transition metal catalysts that can encompass laborious ligand syntheses and (2) limitations in constructing sterically-congested motifs *via* the use of fully-substituted alkenyl electrophiles.[5a,6a,6d] Zaid and coworkers reported a transition metal-free method using stoichiometric base for accessing α-vinylated carbonyl compounds, though the scope of this reaction was limited to minimally substituted styrenes.[8] Despite the existence of the above-mentioned transition metal methodologies, reports of forming quaternary centers *via* α-vinylation of carbonyl compounds are limited and often rely on

the use of less substituted vinyl electrophiles.[6a,c,d,f] Therefore, there is a clear need for new methods to access α-vinylated quaternary centers bearing fully substituted vinyl electrophiles. To note, tetrasubstituted olefins are attractive functional groups in the pharmaceutical industry as they are present in bioactive molecules, such as the anti-cancer agents tamoxifen and etacstil.[9] In analogy to well-established enolate alkylation chemistry and precedent from stoichiometric flash photolysis studies performed by Mayr[10], it was hypothesized that catalytically generated electrophilic vinyl carbocations (**115**) from **114** could be directly trapped by enolate equivalents (**116**) to form α-vinylated carbonyl compounds (**117**) (Scheme 2.4). Mild catalytic methods for the generation of vinyl cations from vinyl sulfonates have been reported recently using lithium/weakly coordinating anion (WCA) salts as the catalyst[11], which are significantly less expensive than transition metals used in previous α-vinylation methods.[12] Moreover, given that increased substitution of vinyl sulfonates enables more facile ionization, it was hypothesized that this approach would allow for the generation of fully-substituted vinyl carbocations that could directly engage in a nucleophilic attack by enolate equivalents.[13,14]

Scheme 2.4. *α-Vinylation of enolate equivalents via vinyl carbocations.*



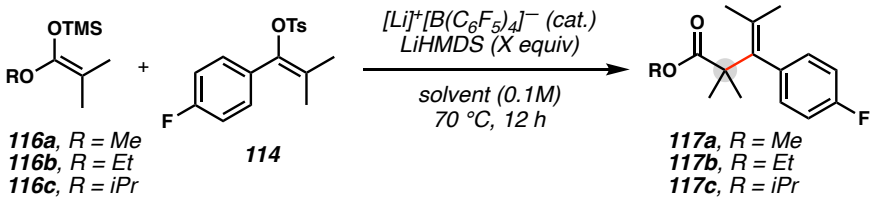
Herein we report a main group-catalyzed α-vinylation reaction to construct highly congested quaternary centers fused to tetrasubstituted olefins. During the late-stage preparation of this manuscript, Chen and coworkers disclosed trapping vinyl cations with silyl enol ethers to access difluoromethylene-skipped enones utilizing squareamide additives; however, though complementary to this report, this method does not appear to enable access to the sterically congested motifs of interest to this study.[15]

2.2 REACTION OPTIMIZATION

With reaction conditions inspired by previous work[11], initial studies commenced with exploring methyl ester silyl ketene acetal **116a** and vinyl tosylate **114**, and gratifyingly, the desired product (**117a**) was observed using 10 mol% $[Li]^+[B(C_6F_5)_4]^-$ with 1.5 equivalents of LiHMDS in *o*-DFB solvent with a 45% yield (Table 2.1, entry 1). We elected to utilize vinyl tosylates as the vinyl cation precursor because they are bench-stable, crystalline solids that could tolerate full substitution on the olefin and electron-rich aromatic moieties, thereby expanding the scope of substrates that could be employed.[11,14,16] The reaction in other solvents, such as *o*-DCB and cyclohexane, was not as efficient (entries 2–3), but when the reaction was performed in $PhCF_3$, a 45% yield was also obtained (entry 4). Product was not observed when the reaction was performed without $[Li]^+[B(C_6F_5)_4]^-$ catalyst (entry 5), but an increase in yield was observed by omitting the use of base (entry 6). Interestingly, in previous studies from our group, a stoichiometric lithium base was required for catalyst turnover.[11,14] The yield was further improved by doubling the equivalents of **116a** (entry 7). Other alkoxy groups on the silyl ketene acetal were also briefly surveyed, and it was found that using ethyl ester derived silyl ketene acetal **116b**

resulted in an improvement in yield (entry 8). However, by implementing a bulkier isopropyl variant (**116c**), a significant drop in yield was observed, likely due to Lewis acid-mediated dealkylation of the silyl ketene acetal and product, supported by mass spectrometry experiments (entry 9).

Table 2.1. *Reaction optimization.*



116a, *R = Me*
116b, *R = Et*
116c, *R = iPr*

114

117a, *R = Me*
117b, *R = Et*
117c, *R = iPr*

Entry	Catalyst	LiHMDS	116	Solvent	R	Yield[a] (%)
1	*10 mol%*	*1.5 equiv*	*1.5 equiv*	*o-DFB*	*Me*	*45%*
2	*10 mol%*	*1.5 equiv*	*1.5 equiv*	*o-DCB*	*Me*	*28%*
3	*10 mol%*	*1.5 equv*	*1.5 equiv*	*CyH*	*Me*	*25%*
4	*10 mol%*	*1.5 equiv*	*1.5 equiv*	*$PhCF_3$*	*Me*	*45%*
5	*0 mol%*	*1.5 equiv*	*1.5 equiv*	*$PhCF_3$*	*Me*	*0%*
6	*10 mol%*	*0 equiv*	*1.5 equiv*	*$PhCF_3$*	*Me*	*56%*
7	*10 mol%*	*0 equiv*	*3 equiv*	*$PhCF_3$*	*Me*	*62%*
8	*10 mol%*	*0 equiv*	*3 equiv*	*$PhCF_3$*	*Et*	*64%*
9	*10 mol%*	*0 equiv*	*3 equiv*	*$PhCF_3$*	*iPr*	*36%*

[a] *Yields determined by ^{19}F NMR using C_6F_6 as an internal standard. OTs, para-toluenesulfonate; o-DFB, 1,2-difluorobenzene; o-DCB, 1,2-dichlorobenzene; CyH, cyclohexane.*

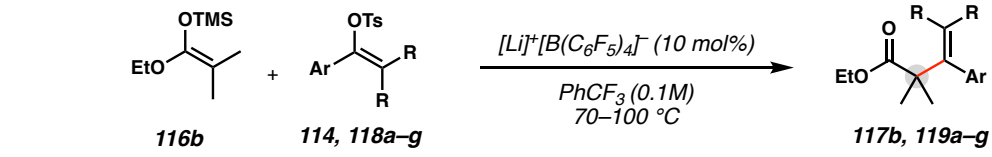
2.3 INVESTIGATION OF SCOPE

2.3.1 Scope of Vinyl Tosylates

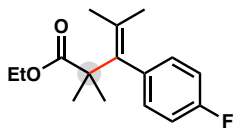
With the optimized reaction conditions in hand, various vinyl tosylates (**114, 118a–g**) were studied for the α-vinylation reaction using ethoxy dimethyl silyl ketene acetal **116b** (Scheme 2.5). α-Vinylated product **117b** was isolated in a 50% yield, which was

diminished from the NMR yield obtained previously (Table 2.1, entry 8). Notably, tetrasubstituted olefins could be constructed, and this methodology tolerates substitution at the vinyl tosylate olefin to access various structures (**119a** and **119b**). More electron-rich vinyl tosylates (**118c** and **118d**) were also tolerated, furnishing products **119c** and **119d** in good yields. The scalability of the reaction was demonstrated by isolating **119c** in 78% yield on a 1.0 mmol scale. Biphenyl product **119e** was also isolated in good yield. Brominated and iodinated substrates (**118f** and **118g**) were also compatible with the reaction conditions, delivering vinylation products **119f** and **119g**, albeit in slightly diminished yields. Current organometallic methods to access α-vinylated carbonyl compounds often rely on the use of palladium and nickel, which are typically incompatible with aryl halides.

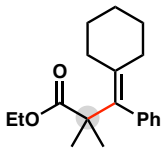
Scheme 2.5. *Scope of vinyl tosylates.*[a]



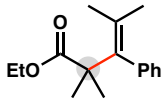
116b + ***114, 118a–g*** → ***117b, 119a–g***



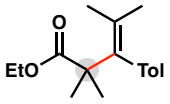
117b, *50% yield (64% yield)*[b]



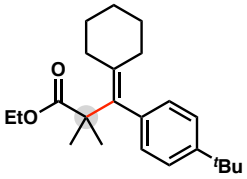
119a, *82% yield*



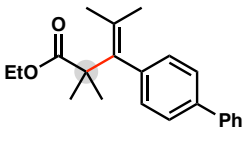
119b, *72% yield*



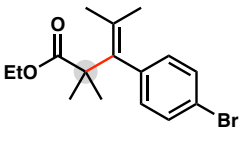
119c, *78% yield*[c] *(1.0 mmol scale)*



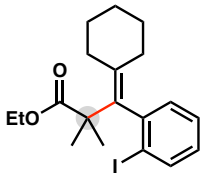
119d, *91% yield*



119e, *87% yield*



119f, *42% yield*



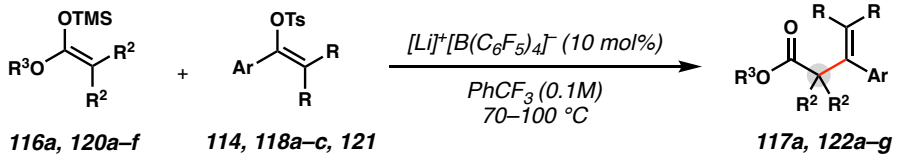
119g, *69% yield*

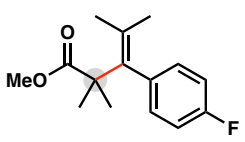
[a]Isolated yield after column chromatography on 0.20 mmol scale with 3 equiv of silyl ketene acetal unless otherwise noted. [b]Yield determined by ^{19}F NMR using C_6F_6 as an internal standard. [c]Reaction performed on 1.0 mmol scale.

2.3.2 Scope of Silyl Ketene Acetals

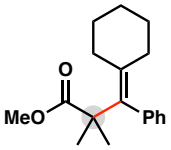
Upon exploration of the vinyl cation precursor, the silyl ketene acetal coupling component was also investigated (Scheme 2.6). Products arising from the α-vinylation of methoxy dimethyl silyl ketene acetal **116a** were isolated in moderate yields (**117a** and **122a**). Moreover, it was found that unsymmetrical silyl ketene acetals **120a** and **120b** afforded products **122b** and **122c** in good yields (70% and 69%, respectively), notably with **122c** possessing a bulky benzyl substituent on the newly formed quaternary center. Additionally, a silyl ketene acetal bearing a cyclic cyclopentyl moiety (**120c**) was also competent in the reaction, which resulted in the formation of product **122d** in 40% yield. These types of sterically encumbered scaffolds (tetrasubstituted olefin fused quaternary centers) are challenging to construct in a concise and catalytic manner, making this a useful method for the construction of α-vinylated quaternary centers. In addition to fully substituted silyl ketene acetals, trisubstituted variants (**120d** and **120e**) also proved successful in this reaction, leading to products **122e** (75% yield) and **122f** (58% yield). A phenyl substituent on the silyl ketene acetal (**120f**) delivered **122g**, albeit in diminished yield. It is important to note that products **122e–g** are isolated without olefin isomerization to the corresponding α,β-unsaturated ester.

Scheme 2.6. *Scope of silyl ketene acetals.*[a]

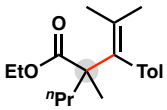




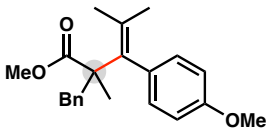
117a, *42% yield (62% yield)*[b]



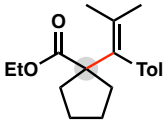
122a*, 80% yield*



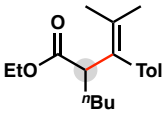
122b*, 70% yield*



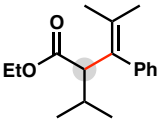
122c*, 69% yield*



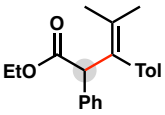
122d*, 40% yield*



122e*, 75% yield*



122f, *58% yield*



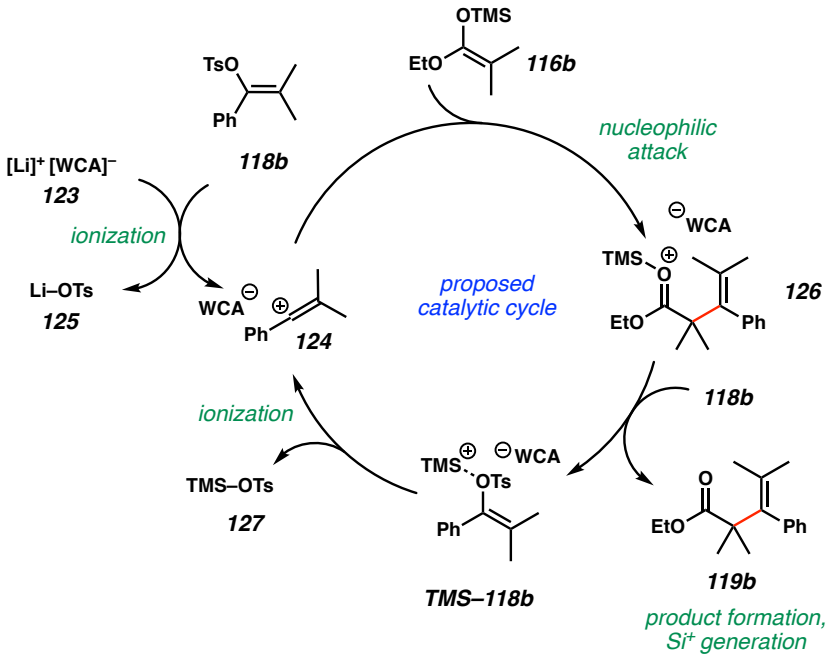
122g, *27% yield*

[a]Isolated yield after column chromatography on 0.20 mmol scale with 3 equiv of silyl ketene acetal unless otherwise noted.
[b]Yield determined by ^{19}F NMR using C_6F_6 as an internal standard.

2.4 MECHANISTIC STUDIES

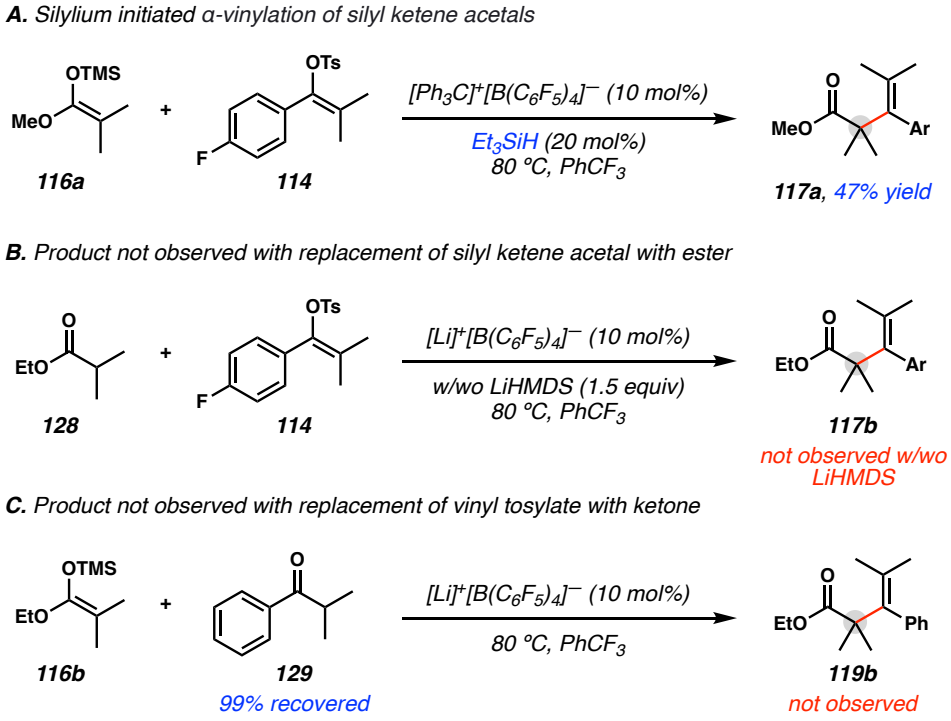
A proposed catalytic cycle is shown in Scheme 2.7. A Lewis acidic Li-based initiator (Li-WCA, **123**) undergoes initial ionization of the vinyl tosylate (**118b**), forming vinyl cation **124** and LiOTs (**125**).[11] Then, nucleophilic attack by silyl ketene acetal **116b** occurs, forming oxocarbenium **126**, forging a new C–C bond and quaternary center. Since a stoichiometric lithium base is not required to obtain the desired product by turning over the catalytic cycle (Table 2.1), an *in situ* generated silyl Lewis acid is postulated to subsequently ionize **118b** to propagate the catalytic cycle to form vinyl cation **124** and TMSOTs (**127**).

Scheme 2.7. *Proposed catalytic cycle for α-vinylation of silyl ketene acetals.*



To probe whether the reaction could be catalyzed by silylium (instead of lithium), silyl ketene acetal **116a** and vinyl tosylate **114** were subjected to silylium/WCA by mixing catalytic $[Ph_3C]^+[B(C_6F_5)_4]^-$ with silane, leading to *in situ* silylium generation via the Bartlett-Condon-Schneider hydride transfer reaction.[17] This delivered the vinylated product **117a**, albeit in a lower yield (Scheme 2.8A). This suggested that lithium is not needed for catalysis and supports that *in situ* silylium generation is a likely operative pathway for this reaction. Attempts to replace the silyl ketene acetal with its corresponding ester (**128**) were unsuccessful, as the desired product was not observed in the presence or absence of a base (Scheme 2.8B). Finally, replacing **118b** with the corresponding isobutyrophenone (**129**) did not lead to the desired product (**119b**) and only starting material was recovered, further supporting the proposed mechanism (Scheme 2.8C).

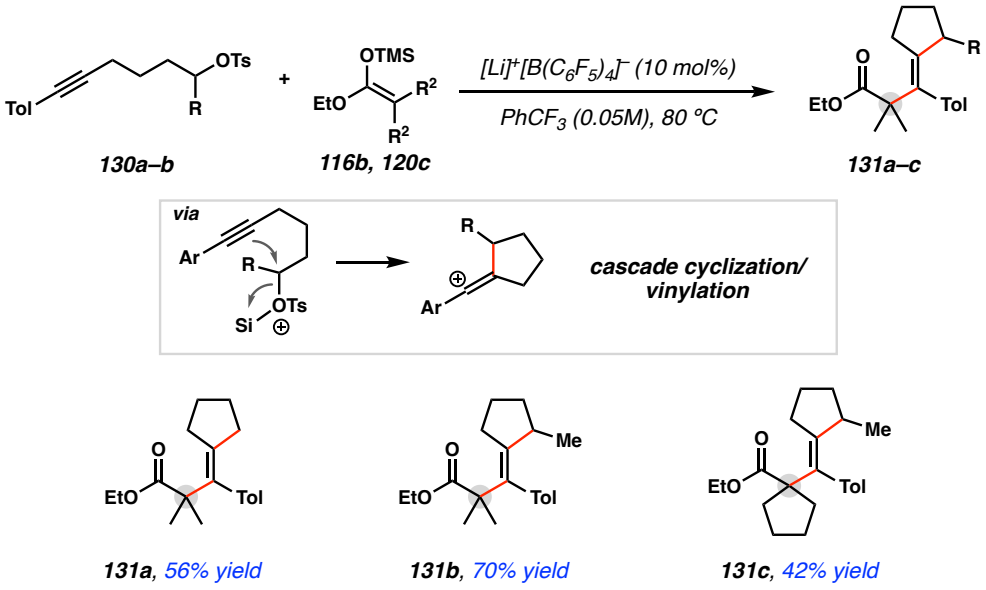
Scheme 2.8. *Control experiments to support the proposed mechanism.*



2.5 INVESTIGATION OF ELECTROPHILIC ADDITION TO ALKYNES

In efforts to study other methods for the generation of vinyl cations that could directly engage in intermolecular α-vinylation, the electrophilic alkylation of alkynes was explored, which has been a reported strategy to access vinyl carbocation intermediates.[18] It was hypothesized that a tethered alkyl chain bearing an appropriate leaving group could be cyclized onto an alkyne through Lewis acid activation of the leaving group, and the resulting vinyl cation could then be trapped by silyl ketene acetals in an intermolecular fashion as discussed above (Scheme 2.9).

Scheme 2.9. *α-Vinylation of esters from alkyne starting materials.*[a]



[a]Isolated yield after column chromatography on 0.20 mmol scale with 3 equiv of silyl ketene.

The alkyne difunctionalization cascade enabled substitution at distal positions of the product to generate further complexity. To this end, it was discovered that alkyne substrates with an appended tosylate group (**130a–b**) could engage in alkyne alkylation/intermolecular nucleophilic trapping cascades to deliver tetrasubstituted olefin products **131a–c** (Scheme 2.9). In the case where a secondary tosylate **130b** was employed, which resulted in an unsymmetrical cyclopentane ring upon cyclization, a single olefin isomer was isolated in good yield for products **131b** and **131c** highlighting a selective addition step to forge tetrasubstituted *E*-olefins. These results highlight an alternative, alkyne difunctionalization approach for accessing sterically congested carbonyl compounds, which complement the vinyl tosylate ionization approach outlined in this study.

2.6 CONCLUDING REMARKS

In conclusion, two main group-catalyzed approaches towards accessing sterically congested α-vinylated ester products through the trapping of vinyl cations with silyl ketene acetals are disclosed. Many of the catalytic approaches towards accessing α-vinylated ester products rely on transition metal catalysis, while here, a simple main group salt is utilized in this transformation. Additionally, methods to construct α-vinylated carbonyl products bearing a tetrasubstituted alkene adjacent to a quaternary center are limited. This study opens the door towards further application of catalytically-generated vinyl cation intermediates in synthesis, as well as offers the possibility to access these products in an asymmetric fashion. Overall, vinyl cations are underutilized reactive intermediates in catalysis, and this work highlights their ability to form sterically congested motifs.

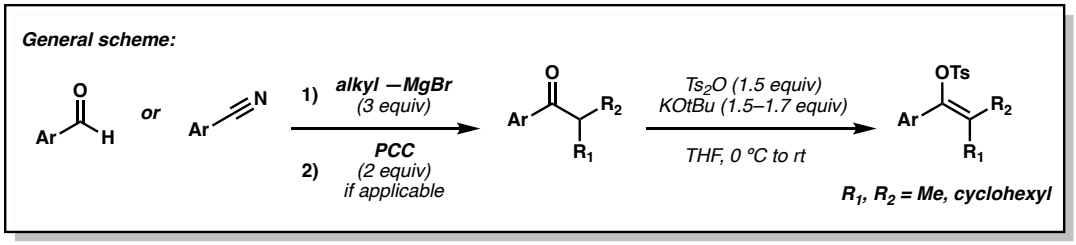
2.7 EXPERIMENTAL SECTION

2.7.1 Materials and Methods

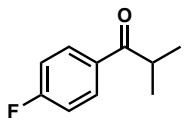
Unless otherwise stated, all reactions were performed in an MBraun or VAC glovebox under nitrogen atmosphere with ≤ 0.5 ppm O_2 levels. All glassware and stir-bars were dried in a 160 °C oven for at least 12 hours and cycled directly into the glovebox for use. Solid substrates were dried on high vacuum over P_2O_5 overnight. All solvents were rigorously dried before use. 1,2-Dichloroethane, benzene, and trifluorotoluene were degassed and dried in a JC Meyer solvent system and stored inside a glovebox. Cyclohexane was distilled over potassium. *o*-Difluorobenzene was distilled over CaH_2. All other solvents used for substrate synthesis were dried in a JC Meyer solvent system. Diisopropylamine was distilled over CaH_2 prior to use. $[Li]^+[B(C_6F_5)_4]^-$ salt was synthesized according to literature procedure.[19] Preparatory thin layer chromatography (TLC) was performed using Millipore silica gel 60 F_{254} pre-coated plates (0.25 mm) and visualized by UV fluorescence quenching. SiliaFlash P60 silica gel (230-400 mesh) was used for flash chromatography. NMR spectra were recorded on a Bruker 400 MHz with Prodigy cryoprobe (^1H, ^{13}C, ^{31}P, ^{11}B), a Bruker 400 MHz (^1H, ^{13}C, ^{19}F), a Varian 300 MHz (^1H, ^{19}F), and a Bruker AV-500 (^1H, ^{13}C). ^1H NMR spectra are reported relative to $CDCl_3$ (7.26 ppm) unless noted otherwise. Data for ^1H NMR spectra are as follows: chemical shift (ppm), multiplicity, coupling constant (Hz), integration. Multiplicities are as follows: s = singlet, d = doublet, t = triplet, dd = doublet of doublet, dt = doublet of triplet, ddd = doublet of doublet of doublet, td = triplet of doublet, qd = quartet of doublets, m = multiplet. Structural assignments were made with additional information from gCOSY, gHSQC, and

gHMBC experiments. ^{13}C NMR spectra are reported relative to $CDCl_3$ (77.1 ppm) unless noted otherwise. IR Spectra were record on a Thermo Scientific Nicolet iS50 FT-IR and are reported in terms of frequency absorption (cm^{-1}). High resolution mass spectra (HR-MS) were recorded on an Agilent 6230 time-of-flight LC/MS (LC/TOF) using electrospray ionization (ESI) or acquired by the Caltech Mass Spectral Facility by Field Ionization/Field Desorption mass spectrometry using a JEOL AccuTOF GC-Alpha (JMS-T2000GC) mass spectrometer interfaced with an Agilent 8890 GC system. Ions were detected as M+. (Radical cations). All commercial chemicals and reagents were used as received, unless otherwise noted. Lithium hexamethyldisilazide was purchased from Sigma Aldrich as a solid and brought in the glovebox as received.

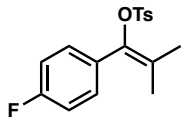
2.7.2 Preparation of Vinyl Tosylates



The procedure outlined above was used to prepare vinyl tosylate substrates from the corresponding ketone, which was either commercially available or synthesized from reported literature procedures through Grignard-addition to the aldehyde or benzonitrile.



1-(4-fluorophenyl)-2-methylpropan-1-one (132) was prepared according to literature procedures and matched the NMR data in the literature.[20]



1-(4-fluorophenyl)-2-methylprop-1-en-1-yl 4-methylbenzenesulfonate (114)

To a flame-dried flask was added **132** (3.00 g, 1.0 equiv, 18.05 mmol) and THF (60.0 mL). This solution was cooled to 0 ºC, and then a solution of KOtBu (3.05 g, 1.5 equiv, 27.1 mmol) in THF (27.0 mL) was added dropwise. The resulting solution was then stirred at 0 ºC for 2 hours. Next, solid Ts_2O (8.84 g, 1.5 equiv, 27.1 mmol) was added to the enolate solution with vigorous stirring, and then the solution was allowed to warm to room temperature and stirred for 1.5 hours (solution turns thick). The reaction was diluted with ethyl acetate (30 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica flash column chromatography (7% diethyl ether in hexanes) to give vinyl tosylate **114** (3.8 g, 66% yield).

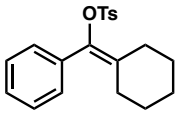
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.3 Hz, 2H), 7.17 – 7.06 (m, 4H), 6.83 (t, *J* = 8.7 Hz, 2H), 2.36 (s, 3H), 1.88 (s, 3H), 1.73 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2 (d, *J* = 248.1 Hz), 144.4, 140.1, 134.3, 131.3 (d, *J* = 8.3 Hz), 130.0 (d, *J* = 3.2 Hz), 129.2, 127.8, 126.7, 114.7 (d, *J* = 21.6 Hz), 21.5, 19.9, 19.0.

^{19}F NMR (282 MHz, $CDCl_3$) δ -112.9.

FT-IR (neat film NaCl): 3069, 2994, 2920, 2861, 1601, 1508, 1366, 1189, 1177, 1082, 995, 844, 784, 669 cm^{-1}.

HR-MS (ESI) m/z: [M+K]+ Calculated for $C_{17}H_{17}FO_3S$ 320.0883; Found 320.0883.



cyclohexylidene(phenyl)methyl 4-methylbenzenesulfonate (118a)

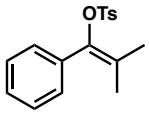
To a flame-dried flask was added commercially available cyclohexyl(phenyl)methanone (2.00 g, 1.0 equiv, 10.6 mmol) and THF (32.0 mL). This solution was cooled to 0 ºC, and then a solution of KOtBu (1.78 g, 1.5 equiv, 15.9 mmol) in THF (15.9 mL) was added dropwise. The resulting solution was then stirred at 0 ºC for 2 hours. Next, solid Ts_2O (5.19 g, 1.5 equiv, 15.9 mmol) was added to the enolate solution with vigorous stirring, and then the solution was allowed to warm to room temperature and stirred for 1.5 hours (solution turns thick). The reaction was diluted with ethyl acetate (50 mL) and water (50 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica flash column chromatography (5% ethyl acetate in hexanes) to give vinyl tosylate **118a** (1.01 g, 28% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.40 (m, 2H), 7.22 – 7.10 (m, 5H), 7.09 – 7.01 (m, 2H), 2.40 (t, *J* = 5.8 Hz, 2H), 2.34 (s, 3H), 2.17 (t, *J* = 5.7 Hz, 2H), 1.65 – 1.46 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.2, 138.8, 134.5, 133.8, 133.6, 129.7, 129.2, 128.04, 128.02, 127.8, 30.0, 28.9, 27.8, 27.2, 26.3, 21.6.

FT-IR (neat film NaCl): 3057, 2929, 2854, 1599, 1446, 1368, 1187, 1176, 1002, 786, 700, 555 cm^{-1}.

HR-MS (ESI) m/z: [M+K]+ Calculated for $C_{20}H_{22}O_3S$ 342.1290; Found 342.1294.



2-methyl-1-phenylprop-1-en-1-yl 4-methylbenzenesulfonate (188b)

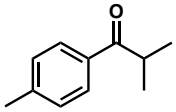
To a flame-dried flask was added commercially available 2-methyl-1-phenylpropan-1-one (2.96 g, 1.0 equiv, 20.0 mmol) and THF (65.0 mL). This solution was cooled to 0 ºC, and then a solution of KOtBu (3.81 g, 1.7 equiv, 34.0 mmol) in THF (34.0 mL) was added dropwise. The resulting solution was then stirred at 0 ºC for 2 hours. Next, a solution of Ts_2O (9.79 g, 1.5 equiv, 30.0 mmol) in THF (50.0 mL) was added to the enolate solution with vigorous stirring, and then the solution was allowed to warm to room temperature and stirred for 1.5 hours (solution turns thick). The reaction was diluted with ethyl acetate (50 mL) and water (50 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica flash column chromatography (10% diethyl ether in hexanes) to give vinyl tosylate **118b** (3.5 g, 58% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.20 – 7.11 (m, 5H), 7.10 – 7.03 (m, 2H), 2.33 (s, 3H), 1.89 (s, 3H), 1.75 (s, 3H).

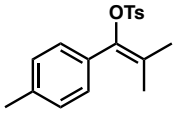
^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3, 141.3, 134.4, 134.0, 129.6, 129.3, 128.0, 127.9, 127.8, 126.5, 21.6, 20.1, 19.2.

FT-IR (neat film NaCl): 3057, 3031, 2995, 2918, 2860, 2860, 1598, 1492, 1444, 1363, 1306, 1272, 1189, 1175, 1085, 1071, 1033, 992, 890, 820, 804, 789, 709, 698, 671, 582, 557, 544 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{17}H_{19}O_3S$ 303.1049; Found 303.1050.



2-methyl-1-(*p*-tolyl)propan-1-one (133) was prepared according to literature procedures and matched the NMR data in the literature.[20]



2-methyl-1-(*p*-tolyl)prop-1-en-1-yl 4-methylbenzenesulfonate (118c)

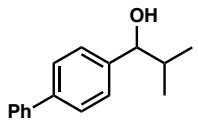
To a flame-dried flask was added **133** (1.64 g, 1.0 equiv, 10.1 mmol) and THF (33.0 mL). This solution was cooled to 0 ºC, and then a solution of KOtBu (1.93 g, 1.7 equiv, 17.2 mmol) in THF (17.2 mL) was added dropwise. The resulting solution was then stirred at 0 ºC for 2 hours. Next, a solution of Ts_2O (4.96 g, 1.5 equiv, 15.2 mmol) in THF (25.3 mL) was added to the enolate solution with vigorous stirring, and then the solution was allowed to warm to room temperature and stirred for 1.5 hours (solution turns thick). The reaction was diluted with ethyl acetate (30 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica flash column chromatography (7% diethyl ether in hexanes) to give vinyl tosylate **118c** (1.2 g, 38% yield).

^{1}H NMR (400 MHz, $CDCl_3$)) δ 7.45 – 7.34 (m, 2H), 7.03 – 6.98 (m, 2H), 6.98 – 6.93 (m, 2H), 6.91 – 6.84 (m, 2H), 2.28 (s, 3H), 2.21 (s, 3H), 1.78 (s, 3H), 1.67 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.2, 141.4, 137.9, 134.6, 131.2, 129.5, 129.2, 128.5, 128.1, 125.9, 21.7, 21.4, 20.2, 19.2.

FT-IR (neat film NaCl): 3029, 2994, 2919, 2861, 1598, 1511, 1449, 1365, 1307, 1189, 1176, 1082, 993, 830, 812, 784, 670, 560 cm^{-1}.

HR-MS (ESI) m/z: [M+Na]+ Calculated for $C_{18}H_{20}NaO_3S$ 339.1025; Found 339.1026.



1-([1,1'-biphenyl]-4-yl)-2-methylpropan-1-ol (134)

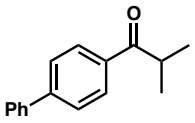
Procedure adapted from the reported literature.[21] To a flame-dried flask was added commercially available [1,1'-biphenyl]-4-carbaldehyde (3.00 g, 1.0 equiv, 16.46 mmol) and THF (16 mL), and this flask was cooled to 0 ºC. Then, 2M isopropylmagnesium chloride (8.2 mL, 1 equiv, 16.46 mmol) was added dropwise and the reaction was allowed to stir at 0 ºC. Upon full consumption of starting material, saturated NH_4Cl was added, and the crude reaction was extracted with ethyl acetate (3x 20 mL). The combined organic layers were washed with water, followed by brine, and then dried with Na_2SO_4 and concentrated *in-vacuo.* Pure material was obtained by silica flash column chromatography (15% ether in hexanes) to afford white solid **134** (1.1 g, 29% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 – 7.62 (m, 4H), 7.50 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.46 – 7.44 (m, 2H), 7.42 – 7.37 (m, 1H), 4.49 (d, *J* = 6.8 Hz, 1H), 2.07 (h, *J* = 6.7 Hz, 1H), 1.10 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.8, 141.0, 140.4, 128.9, 127.4, 127.2, 127.1, 127.0, 79.9, 35.4, 19.2, 18.4.

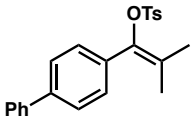
FT-IR (neat film NaCl): 3390, 3056, 3028, 2957, 2870, 1600, 1486, 1468, 1405, 1384, 1365, 1175, 1029, 1016, 1007, 836, 761, 737, 696, 574, 507 cm^{-1}.

HR-MS (ESI) m/z: [M–H_2O]+ Calculated for $C_{16}H_{17}$ 209.1325; Found 209.1329.



1-([1,1'-biphenyl]-4-yl)-2-methylpropan-1-one (135)

To a flame-dried flask was added PCC (2.03 g, 2.0 equiv, 9.43 mmol) and DCM (19 mL). **134** was then added dropwise. The resulting solution was stirred until the starting material was fully consumed, as monitored by TLC. Upon completion, the reaction was plugged through a short silica plug with DCM and then concentrated to afford **135,** which was used without further purification (0.953 g, 90% yield). NMR data matched those reported in the literature.[22]



1-([1,1'-biphenyl]-4-yl)-2-methylprop-1-en-1-yl 4-methylbenzenesulfonate (118e)

To a flame-dried flask was added **135** (0.953 g, 1.0 equiv, 4.25 mmol) and THF (14.2 mL). This solution was cooled to 0 ºC, and then a solution of KOtBu (715 mg, 1.5 equiv, 6.37 mmol) in THF (6.4 mL) was added dropwise. The resulting solution was then stirred at 0 ºC for 2 hours. Next, solid Ts_2O (2.08 g, 1.5 equiv, 6.37 mmol) was added to the enolate solution with vigorous stirring, and then the solution was allowed to warm to room temperature and stirred for 1.5 hours (solution turns thick). The reaction was diluted with ethyl acetate (30 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL), dried over Na_2SO_4, filtered,

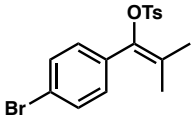
concentrated *in vacuo*, and purified by silica flash column chromatography (15% diethyl ether in hexanes) to give vinyl tosylate **118e** (838 mg, 52% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.49 (m, 2H), 7.49 – 7.42 (m, 4H), 7.38 – 7.32 (m, 3H), 7.21 – 7.16 (m, 2H), 7.08 – 7.01 (m, 2H), 2.29 (s, 3H), 1.93 (s, 3H), 1.82 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7, 140.2, 134.3, 132.9, 131.2, 131.0, 129.4, 128.1, 127.4, 122.2, 21.7, 20.1, 19.2.

FT-IR (neat film NaCl): 3031, 2993, 2918, 2858, 1598, 1486, 1366, 1189, 1176, 1082, 992, 848, 808, 789, 755, 735, 698, 670, 586, 571, 552 cm^{-1}.

HR-MS (ESI) m/z: [M+Na]+ Calculated for C23H22NaO3S 401.1182; Found 401.1184.



1-(4-bromophenyl)-2-methylprop-1-en-1-yl 4-methylbenzenesulfonate (118f)

To a flame-dried flask was added commercially available 1-(4-bromophenyl)-2-methylpropan-1-one (1.00 g, 1.0 equiv, 4.40 mmol) and THF (14.7 mL). This solution was cooled to 0 ºC, and then a solution of KOtBu (741 mg, 1.5 equiv, 6.61 mmol) in THF (6.6 mL) was added dropwise. The resulting solution was then stirred at 0 ºC for 2 hours. Next, solid Ts_2O (2.16 g, 1.5 equiv, 6.61 mmol) was added to the enolate solution with vigorous stirring, and then the solution was allowed to warm to room temperature and stirred for 1.5 hours (solution turns thick). The reaction was diluted with ethyl acetate (30 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by

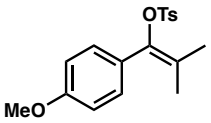
silica flash column chromatography (15% diethyl ether in hexanes) to give vinyl tosylate **118f** (1.2 g, 71% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.3 Hz, 2H), 7.26 – 7.22 (m, 2H), 7.12 – 7.08 (m, 2H), 7.01 – 6.96 (m, 2H), 2.38 (s, 3H), 1.88 (s, 3H), 1.74 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7, 140.2, 134.3, 132.9, 131.2, 131.0, 129.4, 128.0, 127.4, 122.2, 21.7, 20.1, 19.2.

FT-IR (neat film NaCl): 3066, 2991, 2920, 2858, 1597, 1589, 1485, 1448, 1367, 1190, 1175, 1083, 993, 835, 812, 785, 734, 664, 589, 559 cm^{-1}.

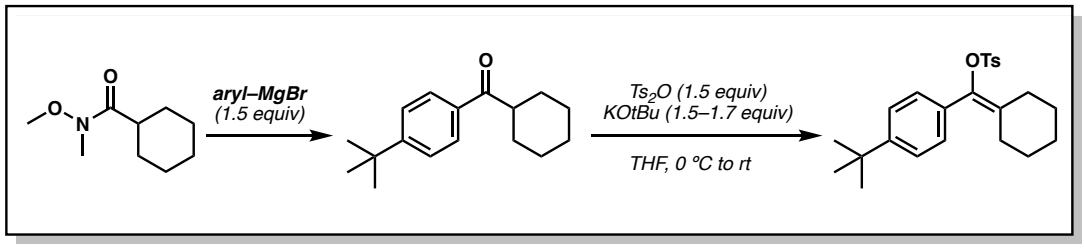
HR-MS (FD) m/z: [M•]+ Calculated for $C_{17}H_{17}BrO_3S$ 380.0076; Found 380.0082.



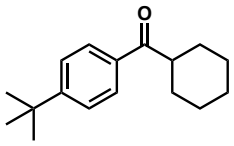
1-(4-methoxyphenyl)-2-methylprop-1-en-1-yl 4-methylbenzenesulfonate (121)

To a flame-dried flask was added commercially available 1-(4-methoxyphenyl)-2-methylpropan-1-one **(**4.80 g, 1.0 equiv, 26.9 mmol) and THF (87 mL). This solution was cooled to 0 ºC, and then a solution of KOtBu (5.14, 1.7 equiv, 45.8 mmol) in THF (46 mL) was added dropwise. The resulting solution was then stirred at 0 ºC for 2 hours. Next, a solution of Ts_2O (13.2 g, 1.5 equiv, 40.4 mmol) in THF (67 mL) was added to the enolate solution with vigorous stirring, and then the solution was allowed to warm to room temperature and stirred for 1.5 hours (solution turns thick). The reaction was diluted with ethyl acetate (30 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica flash column chromatography (15% diethyl

ether in hexanes) to give vinyl tosylate **121** (5.4 g, 60% yield). The purified material matched the NMR data in the literature.[23]



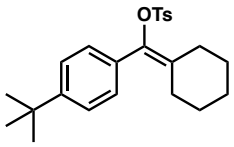
The following vinyl tosylate **118d** was prepared according to the above scheme.



(4-(*tert*-butyl)phenyl)(cyclohexyl)methanone (136)

136 was synthesized by following a reported procedure.[24] To a flask was added magnesium turnings (1.96 g, 1.5 equiv, 80.6 mmol) and the flask was flame-dried 3x under vacuum. THF (81 mL) was then added with a spec of iodine. 1-bromo-4-(tert-butyl)benzene (17.7 mL, 1.9 equiv, 102 mmol) was added, and then the reaction flask was gently heated with a heat gun until the reaction initiated, as indicated by dissipation of iodine color. The reaction was then stirred until all magnesium turnings had been consumed. Upon consumption of magnesium, the reaction was cooled to 0 ºC, and a solution of N-methoxy-N-methylcyclohexanecarboxamide (9.20 g, 1.0 equiv, 53.4 mmol) in THF (179 mL) was added dropwise. Upon consumption of the starting material in about 10 minutes (TLC 60% ethyl acetate in hexanes), saturated NH_4Cl was added to quench the reaction. The reaction was then extracted with ethyl acetate (3x), and the combined organics were washed with

water, then brine, dried with Na_2SO_4, and concentrated *in vacuo.* The crude material was flashed via silica flash column chromatography (20% ethyl acetate in hexanes) to afford colorless oil **136** (4.0 g, 30% yield) which matched reported literature spectra.[25]



(4-(*tert*-butyl)phenyl)(cyclohexylidene)methyl 4-methylbenzenesulfonate (118d)

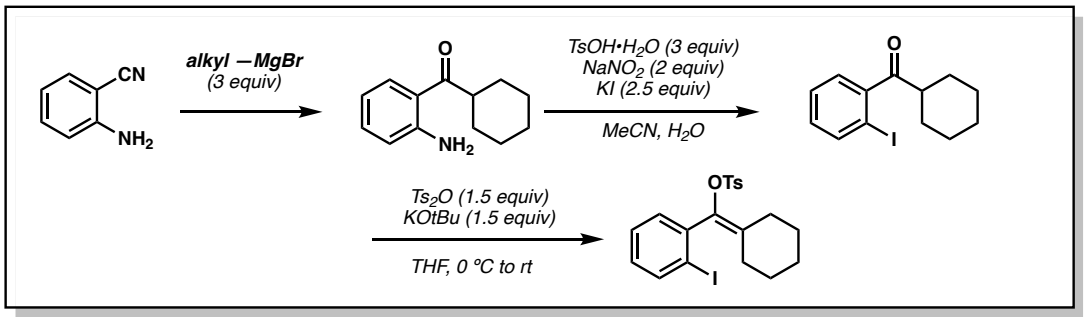
To a flame-dried flask was added **136** (1.00 g, 1.0 equiv, 4.09 mmol) and THF (13.3 mL). This solution was cooled to 0 ºC, and then a solution of KOtBu (689 mg, 1.5 equiv, 6.14 mmol) in THF (6.14 mL) was added dropwise. The resulting solution was then stirred at 0 ºC for 2 hours. Next, solid Ts_2O (2.00 g, 1.5 equiv, 6.14 mmol) was added to the enolate solution with vigorous stirring, and then the solution was allowed to warm to room temperature and stirred for 1.5 hours (solution turns thick). The reaction was diluted with ethyl acetate (30 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica flash column chromatography (7% diethyl ether in hexanes) to give vinyl tosylate **118d** (340 mg, 21% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 2H), 7.10 – 7.06 (m, 2H), 7.02 – 6.96 (m, 4H), 2.48 – 2.43 (m, 2H), 2.30 (s, 3H), 2.17 (s, 2H), 1.65 – 1.50 (m, 6H), 1.25 (s, 9H).

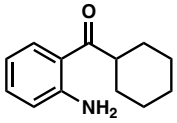
^{13}C NMR (101 MHz, $CDCl_3$) δ 151.0, 143.7, 139.0, 134.8, 133.2, 130.5, 129.4, 129.1, 128.0, 124.6, 34.6, 31.4, 30.1, 29.0, 27.8, 27.3, 26.4, 21.6.

FT-IR (neat film NaCl): 2962, 2929, 2854, 1598, 1449, 1366, 1187, 1175, 1106, 1094, 1021, 1003, 981, 903, 844, 825, 812, 780, 730, 667, 579, 569, 556 cm^{-1}.

HR-MS (ESI) m/z: [M+Na]+ Calculated for $C_{24}H_{30}NaO_3S$ 421.1808; Found 421.1809.

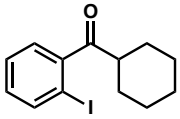


The following vinyl tosylate **118g** was prepared according to the above scheme.



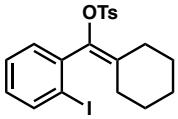
(2-aminophenyl)(cyclohexyl)methanone (137)

Following a reported procedure[26], to a flame-dried flask, 2-aminobenzonitrile (12.0 g, 1.0 equiv, 101.6 mmol) was suspended in THF (101 mL) and the flask was cooled to 0 ºC. Then, 1M cyclohexylmagnesium bromide (290 mL, 3.0 equiv, 305 mmoL) was added dropwise. After addition was complete, the reaction was warmed to room temperature. Starting material was consumed after about 4 hours (monitored by TLC). The reaction was then cooled to 0 ºC, and water was slowly added, followed by conc. HCl. The reaction was then extracted with diethyl ether 3x, and the combined organics were dried with $MgSO_4$ and concentrated. The crude reaction mixture was purified *via* silica flash column chromatography (20% ether/hexanes) to afford **137** (14.9 g, 72% yield). NMR spectra matched those reported in the literature.[26]



cyclohexyl(2-iodophenyl)methanone (138)

Following a reported procedure[27], *p*-toluenesulfonic acid monohydrate (11.2 g, 3.00 equiv, 59.0 mmol) was added to a flask with MeCN (80 mL), followed by **137** (4.00 g, 1.0 equiv, 19.7 mmol). The solution was cooled to 0 ºC, and a solution of $NaNO_2$ (2.71 g, 2.0 equiv, 39.4 mmol) in water (6 mL) was added dropwise over 5 minutes. Then, a solution of KI (8.17 g, 2.50 equiv, 49.2 mmol) in water (8 mL) was added slowly. The reaction was allowed to stir at 0 ºC for 10 additional minutes, then was warmed to room temperature and stirred for 3 hours. Water was then added and then the reaction was basified to pH 9 with saturated $NaHCO_3$. Saturated $Na_2S_2O_3$ was added next. The reaction was then extracted with EtOAc (3x 250 mL), and the combined organic layers were washed with brine and dried with Na_2SO_4, and then concentrated. Pure product **138** was obtained via silica flash column chromatography (2% -->6% diethyl ether in hexanes and matched the reported spectra (5.10 g, 83% yield).[28]



cyclohexylidene(2-iodophenyl)methyl 4-methylbenzenesulfonate (118g)

To a flame-dried flask was added **138** (2.50 g, 1.0 equiv, 7.96 mmol) and THF (30 mL). This solution was cooled to 0 ºC, and then a solution of KOtBu (1.34 g, 1.5 equiv, 11.9 mmol) in THF (45 mL) was added dropwise. The resulting solution was then stirred at 0

ºC for 2 hours. Next, solid Ts_2O (3.90 g, 1.5 equiv, 11.9 mmol) was added to the enolate solution with vigorous stirring, and then the solution was allowed to warm to room temperature and stirred for 1.5 hours (solution turns thick). The reaction was diluted with ethyl acetate (30 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica flash column chromatography (15% diethyl ether in hexanes) to give vinyl tosylate **118g** (3.05 g, 82% yield).

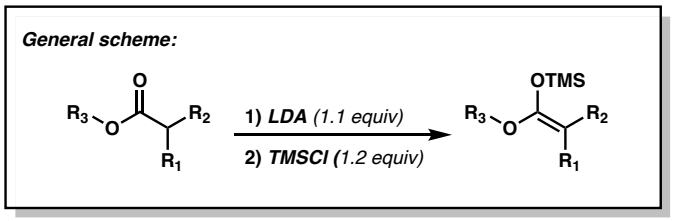
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.52 – 7.47 (m, 2H), 7.23 (dtd, *J* = 15.9, 7.9, 6.3 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.87 (td, *J* = 7.5, 1.9 Hz, 1H), 2.51 (ddd, *J* = 13.6, 6.9, 4.8 Hz, 1H), 2.37 (ddd, *J* = 13.0, 7.6, 4.8 Hz, 1H), 2.33 (s, 3H), 1.93 (t, *J* = 5.8 Hz, 2H), 1.65 (h, *J* = 5.5 Hz, 2H), 1.60 – 1.48 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.1, 139.3, 139.1, 138.7, 135.2, 134.5, 132.9, 129.8, 129.2, 127.8, 127.5, 100.1, 30.3, 28.4, 27.6, 27.1, 26.4, 21.7.

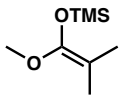
FT-IR (neat film NaCl): 3064, 2927, 2853, 1598, 1460, 1448, 1431, 1364, 1307, 1257, 1232, 1209, 1188, 1175, 1117, 1095, 1051, 1018, 1002, 979, 827 cm^{-1}.

HR-MS (ESI) m/z: [M+Na]+ Calculated for $C_{20}H_{21}INaO_3S$ 491.0148 Observed: 491.0143.

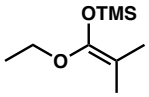
2.7.3 Preparation of Silyl Ketene Acetals



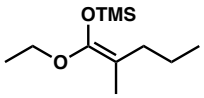
The general reaction scheme outlined above was used to prepare silyl ketene acetals from commercially available esters and was adapted from the literature.[29] To a flame-dried flask was added diisopropylamine (1.1 equiv) and THF (0.66 M) and cooled to 0 ºC. Then, a solution of 2.5 M *n*-Butyllithium (1.1 equiv) was added dropwise, and the solution was allowed to warm to room temperature and stirred for 30 minutes. The reaction was then cooled to -78 ºC and the appropriate ester was added dropwise (1.0 equiv), and the resulting solution was stirred for 1 hour at -78 ºC. TMSCl (1.2 equiv) was subsequently added dropwise at -78 ºC, and the reaction was allowed to slowly warm up to room temperature overnight. The reaction was then concentrated *in-vacuo,* and then pentanes was then added. The suspension was filtered through a pad of celite, concentrated once more, and then distilled for purification to afford colorless oils.



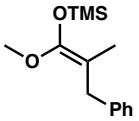
((1-methoxy-2-methylprop-1-en-1-yl)oxy)trimethylsilane (116a) was purchased and used as received.



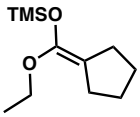
((1-ethoxy-2-methylprop-1-en-1-yl)oxy)trimethylsilane (116b) was prepared according to the described procedure on 30.00 mmol scale (50% yield, 3 g) and matches reported spectra.[30]



((1-ethoxy-2-methylpent-1-en-1-yl)oxy)trimethylsilane (120a) (mixture of E/Z isomers) was prepared according to the described procedure on 30.0 mmol scale (60% yield, 4 g) and obtained as a mixture of *E/Z* isomers (*E/Z* ratio 60:40). The compound matches reported spectra.[31]



((1-methoxy-2-methyl-3-phenylprop-1-en-1-yl)oxy)trimethylsilane (mixture of E/Z isomers) (120b) was prepared according to the described procedure on 12.9 mmol scale (60% yield) with *E/Z* ratio = 6.4:1. The compound matches the reported literature.[32]



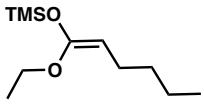
(cyclopentylidene(ethoxy)methoxy)trimethylsilane (120c) was prepared according to the described procedure on 37.3 mmol scale (50% yield, 4 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 – 3.72 (m, 2H), 2.24 – 2.16 (m, 2H), 2.12 (dddd, *J* = 8.3, 4.6, 2.4, 1.0 Hz, 2H), 1.61 – 1.56 (m, 4H), 1.22 (t, *J* = 7.1 Hz, 3H), 0.20 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.9, 102.2, 64.1, 28.4, 27.8, 27.2, 27.0, 15.2, 0.3.

FT-IR (neat film NaCl): 2955, 2898, 2867, 2845, 2357, 1713, 1443, 1389, 1315, 1252, 1232, 1215, 1178, 1150, 1081, 1028, 1005, 949, 875, 845, 756, 697 cm^{-1}.

HR-MS (FI) m/z: [M•]+ Calculated for $C_{11}H_{22}O_2Si$ 214.1402; Found 214.1389.



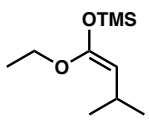
((1-ethoxyhex-1-en-1-yl)oxy)trimethylsilane (120d) (mixture of E/Z isomers) was prepared according to the described procedure on 30.2 mmol scale (60% yield, 4 g) and was obtained as a mixture of *E/Z* isomers (*E/Z* ratio = 94:6). Product was assigned as *E* olefin isomer by comparing to similar silyl ketene acetals.[33]

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (q, *J* = 7.1 Hz, 2H), 3.72 (t, *J* = 7.3 Hz, 1H), 1.99 – 1.93 (m, 2H), 1.31 – 1.25 (m, 4H), 1.22 (t, *J* = 7.1 Hz, 3H), 0.89 (m, 3H), 0.21 (s, 9H).

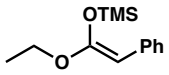
^{13}C NMR (101 MHz, $CDCl_3$) δ 152.8, 87.2, 63.3, 33.2, 24.5, 22.5, 15.2, 14.2, 0.02.

FT-IR (neat film NaCl): 2958, 2932, 2873, 2861, 1737, 1466, 1373, 1251, 1178, 1110, 1038, 845, 729, 677 cm^{-1}.

HR-MS (FI) m/z: [M•]+ Calculated for $C_{11}H_{24}O_2Si$ 216.1540; Found 216.1545.

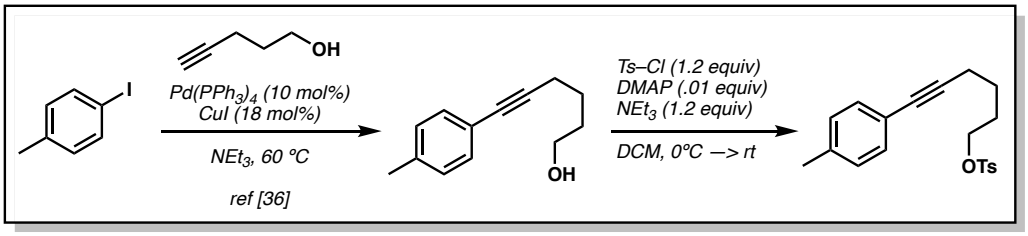


(*E*)-((1-ethoxy-3-methylbut-1-en-1-yl)oxy)trimethylsilane (120e) (mixture of E/Z isomers) was prepared according to the described procedure on 30.0 mmol scale (70% yield) with *E/Z* ratio = 98:2. The compound matches the reported literature.[34]

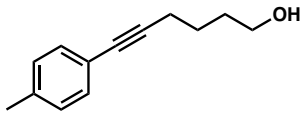


((1-ethoxy-2-phenylvinyl)oxy)trimethylsilane (mixture of E/Z isomers) (120f) was prepared according to the described procedure on 30.0 mmol scale (40% yield) with *E/Z* ratio = 1:21. The compound matches the reported literature.[35]

2.7.4 Preparation of Alkyne Cyclization Substrates

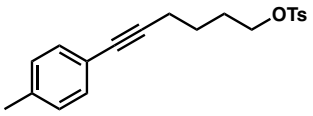


Tosylate **130a** was prepared according to above scheme.



6-(*p*-tolyl)hex-5-yn-1-ol (139)

This compound was prepared according to a reported procedure[36] and all spectra match reported.[37]



6-(*p*-tolyl)hex-5-yn-1-yl 4-methylbenzenesulfonate (130a)

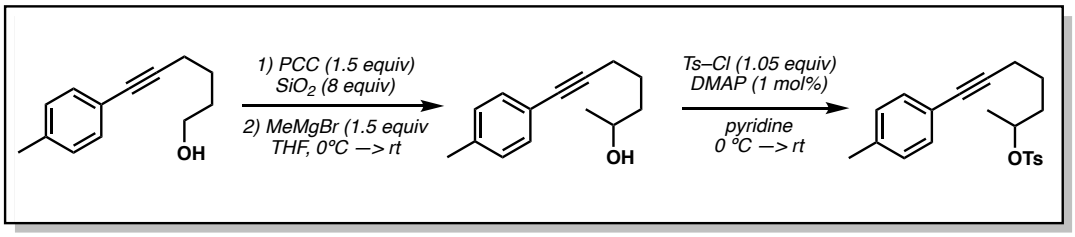
Alcohol **139** (800 mg, 1.0 equiv, 4.25 mmol) was dissolved in dry DCM (30 mL) in a flame-dried flask. The solution was cooled to 0 ºC, then DMAP (5.2 mg, 0.01 equiv, 0.04 mmol) was added, followed by 4-toluenesulfonyl chloride (Ts-Cl) (972 mg, 1.2 equiv, 5.10 mmol) add as solids in one portion. Then, dry (distilled over CaH_2) triethylamine (0.71 mL, 1.2 equiv, 5.10 mmol) was added dropwise. The mixture was allowed to warm to room temperature slowly overnight. The next morning, the reaction was quenched with 1M HCl (aq), and extracted with DCM three times. The combines organics were dried over Na_2SO_4, filtered, concentrated, then purified *via* silica column flash chromatography (10% ethyl acetate in hexanes) to afford pure tosylate **130a** (1.0 g, 69% yield) as a thick colorless oil which solidifies upon cooling.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.84 – 7.76 (m, 2H), 7.38 – 7.29 (m, 2H), 7.29 – 7.21 (m, 2H), 7.12 – 7.05 (m, 2H), 4.09 (t, *J* = 6.3 Hz, 2H), 2.44 (s, 3H), 2.37 (t, *J* = 6.9 Hz, 2H), 2.33 (s, 3H), 1.83 (tt, *J* = 8.1, 6.0 Hz, 2H), 1.68 – 1.57 (m, 2H).

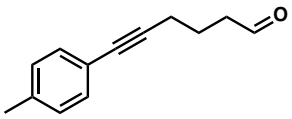
^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8, 137.8, 133.2, 131.5, 129.9, 129.1, 128.0, 120.7, 88.2, 81.4, 70.2, 28.1, 24.7, 21.7, 21.5, 18.8.

FT-IR (neat film NaCl): 2951, 2922, 1509, 1355, 1188, 1172, 1097, 1019, 813, 689, 661, 552, 525 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{20}H_{23}O_3S^+$: 343.1368; Found 343.1366.

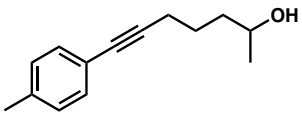


Tosylate **130b** was prepared according to the above scheme.



6-(*p*-tolyl)hex-5-ynal (140)

Following a reported procedure.[38] To a flame-dried flask containing silica gel (2.0 g) and PCC (1.37g, 1.5 equiv, 6.37 mmol) was added dry DCM (50 mL). Then, a solution of alcohol **139** (800 mg, 1.0 equiv, 4.25 mmol) dissolved in 10 mL dry DCM was added dropwise. The reaction flask was sealed and heated to 35 ºC overnight. The next morning, the reaction mixture was filtered through a pad of silica and washed through with DCM. The filtrate was concentrated, affording analytically pure (by NMR) material (**140**) that matched reported literature[38] and was taken forward as is.



7-(*p*-tolyl)hept-6-yn-2-ol (141)

Aldehyde **140** (600 mg, 1.0 equiv, 3.22 mmol) was dissolved in 10 mL dry THF in a flame-dried Schlenk flask then cooled to 0 ºC. A solution of methylmagnesium bromide (1.6 mL, 1.5 equiv, 4.8 mmol) in THF (3 M solution) was added dropwise. After warming to room

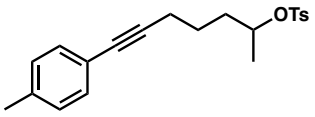
temperature for 30 minutes, the reaction was complete by TLC analysis and was quenched with saturated ammonium chloride. The mixture was extracted with diethyl ether three times, and the combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel flash chromatography (20% ethyl acetate in hexanes) afforded pure alcohol (**141**) as a colorless oil (460 mg, 71% yield).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 2H), 7.09 (ddt, *J* = 7.2, 1.5, 0.8 Hz, 2H), 3.88 (h, *J* = 6.1 Hz, 1H), 2.44 (t, *J* = 6.7 Hz, 2H), 2.33 (s, 3H), 1.82 – 1.55 (m, 4H), 1.23 (dd, *J* = 6.1, 0.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5, 131.4, 128.9, 89.1, 80.9, 67.7, 38.4, 25.0, 23.6, 21.4, 19.4.

FT-IR (neat film NaCl): 3351, 2964, 2924, 2886, 1509, 1455, 1373, 1176, 1105, 1085, 979, 942, 816, 525 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{14}H_{19}O^+$: 203.1430: Found 203.1439.



7-(*p*-tolyl)hept-6-yn-2-yl 4-methylbenzenesulfonate (130b)

Alcohol **141** (385 mg, 1.0 equiv, 1.9 mmol) was dissolved in 1.2 mL dry pyridine (distilled over CaH_2) in an oven-dried dram vial equipped with a stir bar. The vial was cooled to 0 ºC, then DMAP (0.2 mg, .1 mol%, 0.002 mmol) was added followed by tosyl chloride (381 mg, 1.05 equiv, 2.0 mmol) as a solid. The mixture was stirred for 1 hour at 0 ºC then allowed to warm to room temperature overnight. The next morning, the mixture was filtered and diluted with cold diethyl ether and cold 4M HCl (aq). After vigorously shaking

this mixture, the organic layer was removed and the aqueous layer was extracted with cold diethyl ether twice more. The combined organics were washed with cold 4M HCl twice more, then washed with water twice, then washed with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification *via* silica gel flash chromatography (10% ethyl acetate in hexanes) afforded tosylate **130b** as a colorless oil (435 mg, 64% yield).

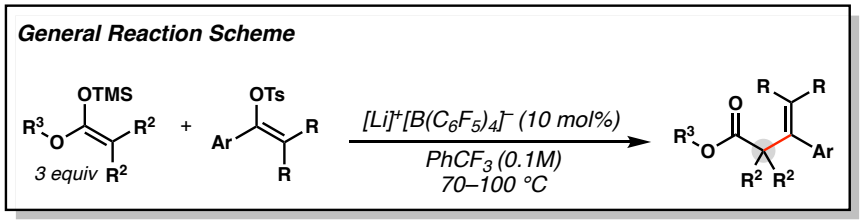
^{1}H NMR (400MHz, $CDCl_3$) δ 7.74 – 7.67 (m, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.17 (m, 2H), 7.02 – 6.95 (m, 2H), 4.64 – 4.51 (m, 1H), 2.31 (s, 3H), 2.25 – 2.18 (m, 5H), 1.71 – 1.54 (m, 2H), 1.53 – 1.33 (m, 2H), 1.19 (d, J = 6.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.6, 137.7, 134.5, 131.5, 129.9, 129.1, 127.8, 120.8, 88.4, 81.3, 80.1, 35.7, 24.2, 21.7, 21.5, 21.0, 19.0.

FT-IR (neat film NaCl): 2935, 2868, 1598, 1509, 1453, 1354, 1188, 1174, 1098, 1043, 893, 816, 663, 577, 556 cm^{-1}.

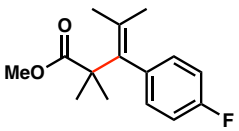
HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{21}H_{25}O_3S^+$: 357.1524 ; Found 357.1519.

2.7.5 α-Vinylation of Silyl Ketene Acetals



General Procedure 1*:* All reactions were conducted in a well-maintained glove box (O_2, H_2O <0.5 ppm) on 0.2 mmol scale unless otherwise noted. To an oven dried dram vial with a magnetic stir bar was added $[Li]^+[B(C_6F_5)_4]^-$ (13.7 mg, 0.02 mmol, 0.1 equiv). To this

was added trifluorotoluene (2 mL), and the corresponding silyl ketene acetal (3 equiv). Substrate (0.2 mmol, 1.0 equiv) was added and the reaction was allowed to stir at 80 °C in a metal heating block placed on an IKA hot plate for 12 hours (unless otherwise noted). The reactions were monitored by TLC, typically using 10% diethyl ether in hexanes for the mobile phase and stained with $KMnO_4$ (α-vinylation products are typically higher in R_f than the starting tosylate and are very distinguishable when stained with $KMnO_4$). Upon completion of reaction, the reaction mixture was removed from the glovebox and diluted with ether containing a drop of triethylamine. This was pushed through a plug of triethylamine treated silica gel in a pipette. The reaction mixture was concentrated in vacuo to give the crude material. The crude material was purified by silica flash chromatography on triethylamine treated silica gel (typically 100% hexanes with 0.1%TEA → 1% diethyl ether in hexanes with 0.1% TEA → 2% diethyl ether in hexanes with 0.1% TEA) and then dried on high vacuum to obtain material that is pure by ^1H NMR.



methyl 3-(4-fluorophenyl)-2,2,4-trimethylpent-3-enoate (117a)

Following General Procedure 1: To an oven dried dram vial with a magnetic stir bar was added $[Li]^+[B(C_6F_5)_4]^-$ (13.7 mg, 0.02 mmol, 0.1 equiv). To this was added trifluorotoluene (2 mL), and silyl ketene acetal **116a** (105 mg, 0.60 mmol, 3 equiv). Vinyl tosylate **114** (64.1 mg, 0.2 mmol, 1.0 equiv) was added and the reaction was allowed to stir at 80 °C in a metal heating block placed on an IKA hot plate for 12 hours. The reaction mixture was

removed from the glovebox and diluted with ether containing a drop of triethylamine. This was pushed through a plug of triethylamine treated silica gel in a pipette and concentrated *in vacuo* to give the crude material. The crude material was purified by silica flash chromatography on triethylamine treated silica gel (2% diethyl ether in hexanes with 0.1% TEA) to give a colorless oil **117a** (21.0 mg, 42% yield).

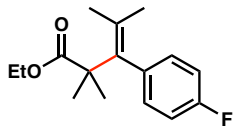
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 – 6.96 (m, 4H), 3.73 (s, 3H), 1.65 (s, 3H), 1.36 (s, 3H), 1.15 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 179.6, 161.5 (d, J = 244.2 Hz), 138.3 (d, J = 3.4 Hz), 137.6, 131.1, 131.0 (d, J = 7.6 Hz), 114.9 (d, J = 21.0 Hz), 52.3, 45.9, 27.6, 23.9, 20.7.

^{19}F NMR (282 MHz, $CDCl_3$) δ -116.9.

FT-IR (neat film NaCl): 2976, 2948, 2873, 1731, 1601, 1506, 1251, 1220, 1138, 844, 584, 337.

HR-MS (ESI) m/z: [M+K]+ Calculated for $C_{15}H_{20}FO_2$ 251.1447; Found 251.1445.



ethyl 3-(4-fluorophenyl)-2,2,4-trimethylpent-3-enoate (117b)

Following General Procedure 1: To an oven dried dram vial with a magnetic stir bar was added $[Li]^+[B(C_6F_5)_4]^-$ (13.7 mg, 0.02 mmol, 0.1 equiv). To this was added trifluorotoluene (2 mL), and the silyl ketene acetal **116b** (113 mg, 0.60 mmol, 3 equiv). Vinyl tosylate **114** (64.1 mg, 0.2 mmol, 1.0 equiv) was added and the reaction was allowed to stir at 80 °C in metal heating block placed on an IKA hot plate for 12 hours. The reaction mixture was

removed from the glovebox and diluted with ether containing a drop of triethylamine. This was pushed through a plug of triethylamine treated silica gel in a pipette and concentrated *in vacuo* to give the crude material. The crude material was purified by silica flash chromatography on triethylamine treated silica gel (2% diethyl ether in hexanes with 0.1% TEA) to give a colorless oil **3b** (26.5 mg, 50% yield).

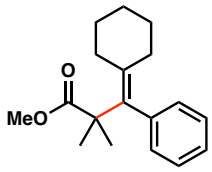
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 – 6.92 (m, 4H), 4.18 (q, J = 7.1 Hz, 2H), 1.66 (s, 3H), 1.35 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.14 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 179.0, 161.5 (d, J = 244.2 Hz), 138.5 (d, J = 3.6 Hz), 137.7, 131.0, 130.9 (d, J = 7.7 Hz), 114.8 (d, J = 21.0 Hz), 60.8, 45.9, 27.6, 23.9, 20.9, 14.4.

^{19}F NMR (282 MHz, $CDCl_3$) δ -117.1.

FT-IR (neat film NaCl): 2977, 2934, 2873, 1726, 1600, 1506, 1469, 1383, 1249, 1219, 1172, 1155, 1136, 1090, 1028, 857, 830, 810, 774, 733, 584, 538 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ $C_{16}H_{22}FO_2$ 265.1598; Found 265.1603.



methyl 3-cyclohexylidene-2,2-dimethyl-3-phenylpropanoate (122a)

Following General Procedure 1: To an oven dried dram vial with a magnetic stir bar was added $[Li]^+[B(C_6F_5)_4]^-$ (13.7 mg, 0.02 mmol, 0.1 equiv). To this was added trifluorotoluene (2 mL), and silyl ketene acetal **116a** (105 mg, 0.60 mmol, 3 equiv). Vinyl tosylate **118a** (68.5 mg, 0.2 mmol, 1.0 equiv) was added and the reaction was allowed to stir at 80 °C in metal heating block placed on an IKA hot plate for 12 hours. The reaction mixture was

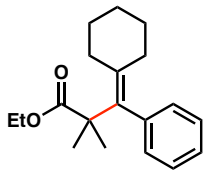
removed from the glovebox and diluted with ether containing a drop of triethylamine. This was pushed through a plug of triethylamine treated silica gel in a pipette and concentrated *in vacuo* to give the crude material. The crude material was purified by silica flash chromatography on triethylamine treated silica gel (2% diethyl ether in hexanes with 0.1% TEA) to give a colorless oil **122a** (43.5 mg, 80% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 2H), 7.24 – 7.16 (m, 1H), 7.13 – 6.95 (m, 2H), 3.73 (s, 3H), 2.09 –2.07 (m, 2H), 1.74 – 1.68 (m, 2H), 1.57 – 1.44 (m, 4H), 1.40 – 1.32 (m, 2H), 1.15 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 180.1, 142.1, 138.3, 135.6, 129.5, 127.9, 126.1, 52.2, 45.6, 33.8, 31.2, 28.4, 28.0, 27.6, 26.8.

FT-IR (neat film NaCl): 3054, 3018, 2974, 2924, 2852, 1728, 1457, 1443, 1249, 1137, 1129, 774, 761, 703 cm^{-1}.

HR-MS (ESI) m/z: [M+K]+ Calculated for $C_{18}H_{25}O_2$ 273.1855; Found 273.1846.



ethyl 3-cyclohexylidene-2,2-dimethyl-3-phenylpropanoate (119a)

Following General Procedure 1: To an oven dried dram vial with a magnetic stir bar was added $[Li]^+[B(C_6F_5)_4]^-$ (13.7 mg, 0.02 mmol, 0.1 equiv). To this was added trifluorotoluene (2 mL), and the silyl ketene acetal **116b** (113 mg, 0.60 mmol, 3 equiv). Vinyl tosylate **118a** (68.5 mg, 0.2 mmol, 1.0 equiv) was added and the reaction was allowed to stir at 80 °C in metal heating block placed on an IKA hot plate for 12 hours. The reaction mixture was

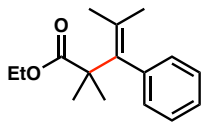
removed from the glovebox and diluted with ether containing a drop of triethylamine. This was pushed through a plug of triethylamine treated silica gel in a pipette and concentrated *in vacuo* to give the crude material. The crude material was purified by silica flash chromatography on triethylamine treated silica gel (2% diethyl ether in hexanes with 0.1% TEA) to give a colorless oil **119a** (47.0 mg, 82% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 2H), 7.25 – 7.20 (m, 1H), 7.10 – 7.00 (m, 2H), 4.17 (q, J = 7.1 Hz, 2H), 2.11 (m, 2H), 1.78 – 1.66 (m, 2H), 1.58 – 1.45 (m, 4H), 1.42 – 1.34 (q, J = 6.1 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H), 1.15 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 179.5, 142.3, 138.2, 135.8, 129.5, 127.9, 126.1, 60.7, 45.6, 33.8, 31.3, 28.4, 28.1, 27.6, 26.8, 14.4.

FT-IR (neat film NaCl): 3054, 2975, 2925, 2852, 1725, 1489, 1468, 1444, 1383, 1363, 1293, 1248, 1171, 1155, 1137, 1030, 853, 774, 760, 704, 531, 406 cm^{-1}.

HR-MS (ESI) m/z: [M+Na]+ Calculated for $C_{19}H_{26}NaO_2$ 309.1825; Found 309.1818.



ethyl 2,2,4-trimethyl-3-phenylpent-3-enoate (119b)

Following General Procedure 1: To an oven dried dram vial with a magnetic stir bar was added $[Li]^+[B(C_6F_5)_4]^-$ (13.7 mg, 0.02 mmol, 0.1 equiv). To this was added trifluorotoluene (2 mL), and the silyl ketene acetal **116b** (113 mg, 0.60 mmol, 3 equiv). Vinyl tosylate **118b** (60.5 mg, 0.2 mmol, 1.0 equiv) was added and the reaction was allowed to stir at 80 °C in metal heating block placed on an IKA hot plate for 12 hours. The reaction mixture was removed from the glovebox and diluted with ether containing a drop of triethylamine. This

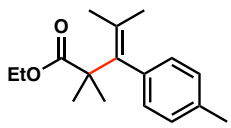
was pushed through a plug of triethylamine treated silica gel in a pipette and concentrated *in vacuo* to give the crude material. The crude material was purified by silica flash chromatography on triethylamine treated silica gel (2% diethyl ether in hexanes with 0.1% TEA) to give a colorless oil **119b** (35.0 mg, 72% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 7.25 – 7.20 (m, 1H), 7.08 – 7.01 (m, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 1.67 (s, 3H), 1.36 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.16 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 179.2, 142.7, 138.7, 130.1, 129.5, 128.0, 126.1, 60.7, 45.9, 27.6, 23.9, 20.9, 14.4.

FT-IR (neat film NaCl): 3055, 2977, 2933, 2872, 1727, 1490, 1469, 1443, 1383, 1362, 1249, 1137, 1085, 1029, 933, 862, 775, 764, 703, 632, 455 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{16}H_{23}O_2$ 247.1693; Found 247.1701.



ethyl 2,2,4-trimethyl-3-(*p*-tolyl)pent-3-enoate (119c)

Following General Procedure 1 with slight modifications; performed on 1.0 mmol scale: To a flame dried 50 mL Schlenk flask with a magnetic stirbar which was brough inside a glovebox, was added $[Li]^+[B(C_6F_5)_4]^-$ (68.6 mg, 0.10 mmol, 0.1 equiv). To this was added trifluorotoluene (10 mL), and the silyl ketene acetal **116b** (565 mg, 3.0 mmol, 3 equiv). Vinyl tosylate **118c** (316 mg, 1.0 mmol, 1.0 equiv) was added. The reaction was then sealed with a glass stopper and heated outside the glovebox at 80 ºC in an oil bath for 12 hours. The reaction mixture was then cooled to room temperature and diluted with ether

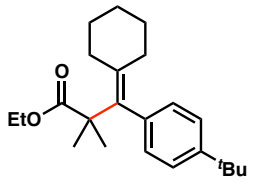
containing 1% triethylamine. This was pushed through a small plug of triethylamine treated silica gel and concentrated *in vacuo* to give the crude material. The crude material was purified by silica flash chromatography on triethylamine treated silica gel (3% diethyl ether in hexanes with 0.1% TEA) to give a colorless oil **119c** (200 mg, 78% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 – 7.08 (m, 2H), 6.96 – 6.88 (m, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.35 (s, 3H), 1.66 (s, 3H), 1.36 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.15 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 179.3, 139.6, 138.5, 135.5, 130.1, 129.4, 128.6, 60.7, 45.9, 27.6, 23.9, 21.3, 20.9, 14.4.

FT-IR (neat film NaCl): 2976, 2931, 2871, 1727, 1510, 1468, 1446, 1382, 1248, 1136, 1028, 932, 856, 815, 731, 529, 485 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{17}H_{25}O_2$ 261.1849; Found 261.1862.



ethyl 3-(4-(*tert*-butyl)phenyl)-3-cyclohexylidene-2,2-dimethylpropanoate (119d)

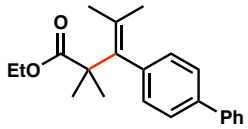
Following General Procedure 1: To an oven dried dram vial with a magnetic stir bar was added $[Li]^+[B(C_6F_5)_4]^-$ (13.7 mg, 0.02 mmol, 0.1 equiv). To this was added trifluorotoluene (2 mL), and the silyl ketene acetal **116b** (113 mg, 0.60 mmol, 3 equiv). Vinyl tosylate **118d** (79.7 mg, 0.2 mmol, 1.0 equiv) was added and the reaction was allowed to stir at 80 °C in a metal heating block placed on an IKA hot plate for 12 hours. The reaction mixture was removed from the glovebox and diluted with ether containing a drop of triethylamine. This was pushed through a plug of triethylamine treated silica gel in a pipette and concentrated *in vacuo* to give the crude material. The crude material was purified by silica flash chromatography on triethylamine treated silica gel (2% diethyl ether in hexanes with 0.1% TEA) to give a colorless oil **119d** (62.0 mg, 91% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.1 Hz, 3H), 6.95 (d, *J* = 7.9 Hz, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 2.09 (t, *J* = 5.6 Hz, 2H), 1.75 – 1.71 (m, 2H), 1.51 (dd, *J* = 8.4, 3.2 Hz, 3H), 1.37 (q, *J* = 5.9 Hz, 2H), 1.32 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 4H), 1.14 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 179.7, 148.7, 139.1, 138.0, 135.7, 129.0, 124.6, 60.7, 45.7, 34.5, 33.8, 31.6, 31.3, 28.5, 28.1, 27.6, 26.8, 14.4.

FT-IR (neat film NaCl): 3023, 2967, 2927, 2853, 1726, 1507, 1467, 1446, 1383, 1363, 1267, 1249, 1138, 1112, 1029, 853, 834, 805, 574, 409 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{23}H_{35}O_2$ 343.2632; Found 343.2633.



ethyl 3-([1,1'-biphenyl]-4-yl)-3-cyclohexylidene-2,2-dimethylpropanoate (119e)

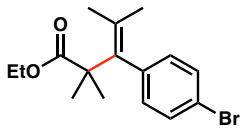
Following General Procedure 1: To an oven dried dram vial with a magnetic stir bar was added $[Li]^+[B(C_6F_5)_4]^-$ (13.7 mg, 0.02 mmol, 0.1 equiv). To this was added trifluorotoluene (2 mL), and the silyl ketene acetal **116b** (113 mg, 0.60 mmol, 3 equiv). Vinyl tosylate **118e** (75.7 mg, 0.2 mmol, 1.0 equiv) was added and the reaction was allowed to stir at 80 °C in a metal heating block placed on an IKA hot plate for 12 hours. The reaction mixture was removed from the glovebox and diluted with ether containing a drop of triethylamine. This was pushed through a plug of triethylamine treated silica gel in a pipette and concentrated *in vacuo* to give the crude material. The crude material was purified by silica flash chromatography on triethylamine treated silica gel (2% diethyl ether in hexanes with 0.1% TEA) to give a colorless oil **119e** (56.0 mg, 87% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.61 (m, 2H), 7.58 – 7.54 (m, 2H), 7.44 (t, J = 7.7 Hz, 2H), 7.33 (td, J = 7.2, 1.3 Hz, 1H), 7.15 – 7.09 (m, 2H), 4.21 (q, J = 7.1 Hz, 2H), 1.70 (s, 3H), 1.42 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.20 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 179.2, 141.8, 141.1, 138.9, 138.3, 130.4, 130.0, 128.9, 127.2, 127.1, 126.6, 60.8, 45.9, 27.7, 24.0, 20.9, 14.6.

FT-IR (neat film NaCl): 3056, 3026, 2976, 2933, 2908, 2872, 1725, 1600, 1485, 1468, 1447, 1383, 1249, 1136, 1028, 1008, 933, 859, 767, 737, 697, 567, 435, 409 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{22}H_{27}O_2$ 323.2006; Found 323.2017.



ethyl 3-(4-bromophenyl)-2,2,4-trimethylpent-3-enoate (119f)

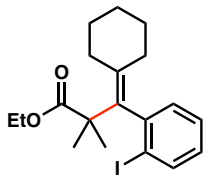
Following General Procedure 1: To an oven dried dram vial with a magnetic stir bar was added $[Li]^+[B(C_6F_5)_4]^-$ (13.7 mg, 0.02 mmol, 0.1 equiv). To this was added trifluorotoluene (2 mL), and the silyl ketene acetal **116b** (113 mg, 0.60 mmol, 3 equiv). Vinyl tosylate **118f** (76.3 mg, 0.2 mmol, 1.0 equiv) was added and the reaction was allowed to stir at 100 °C in a metal heating block placed on an IKA hot plate for 12 hours. The reaction mixture was removed from the glovebox and diluted with ether containing a drop of triethylamine. This was pushed through a plug of triethylamine treated silica gel in a pipette and concentrated *in vacuo* to give the crude material. The crude material was purified by silica flash chromatography on triethylamine treated silica gel (2% diethyl ether in hexanes with 0.1% TEA) to give a colorless oil **119f** (27.0 mg, 42% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 8.4, 1.7 Hz, 2H), 6.93 (dd, *J* = 8.2, 1.8 Hz, 2H), 4.18 (qd, *J* = 7.1, 1.4 Hz, 2H), 1.66 (s, 3H), 1.35 (s, 3H), 1.29 (dd, *J* = 7.7, 6.1 Hz, 3H), 1.14 (d, *J* = 1.8 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 178.9, 141.6, 137.5, 131.3, 131.2, 131.0, 120.2, 60.8, 45.7, 27.6, 23.9, 20.9, 14.4.

FT-IR (neat film NaCl): 2976, 2932, 2872, 1726, 1483, 1469, 1383, 1248, 1136, 1028, 1012, 932, 819, 731, 689, 523, 419 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{16}H_{22}BrO_2$ 325.0798; Found 325.0802.



ethyl 3-cyclohexylidene-3-(2-iodophenyl)-2,2-dimethylpropanoate (119g)

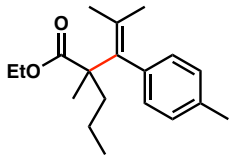
Following General Procedure 1: To an oven dried dram vial with a magnetic stir bar was added $[Li]^+[B(C_6F_5)_4]^-$ (13.7 mg, 0.02 mmol, 0.1 equiv). To this was added trifluorotoluene (2 mL), and the silyl ketene acetal **116b** (113 mg, 0.60 mmol, 3 equiv). Vinyl tosylate **118g** (93.7 mg, 0.2 mmol, 1.0 equiv) was added and the reaction was allowed to stir at 80 °C in a metal heating block placed on an IKA hot plate for 12 hours. The reaction mixture was removed from the glovebox and diluted with ether containing a drop of triethylamine. This was pushed through a plug of triethylamine treated silica gel in a pipette and concentrated *in vacuo* to give the crude material. The crude material was purified by silica flash chromatography on triethylamine treated silica gel (2% diethyl ether in hexanes with 0.1% TEA) to give a colorless oil **119g** (56.7 mg, 69% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.29 (td, *J* = 7.4, 1.2 Hz, 1H), 7.22 (dd, *J* = 7.7, 1.9 Hz, 1H), 6.97 – 6.85 (m, 1H), 4.22 – 4.15 (m, 2H), 2.16 (dqt, *J* = 10.2, 6.9, 3.8 Hz, 2H), 1.77 – 1.57 (m, 5H), 1.51 (m 6H), 1.33 (d, *J* = 7.1 Hz, 3H), 1.06 (s, 3H). **note: one of the methyl peaks is buried with other peaks at 1.51 ppm.*

^{13}C NMR (101 MHz, $CDCl_3$) δ 179.2, 147.6, 139.8, 139.0, 136.6, 130.8, 127.9, 127.7, 102.0, 60.9, 45.8, 33.7, 31.4, 28.6, 27.70, 27.68, 27.2, 26.7, 14.5.

FT-IR (neat film NaCl): 3056, 2978, 2927, 2853, 1724, 1635, 1461, 1445, 1384, 1244, 1138, 1030, 1013, 856, 756, 733, cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{19}H_{26}IO_2$ 413.0972; Found 413.0986.



ethyl 2,4-dimethyl-2-propyl-3-(*p*-tolyl)pent-3-enoate (122b)

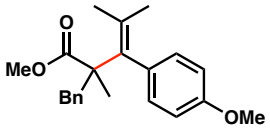
Following General Procedure 1: To an oven dried dram vial with a magnetic stir bar was added $[Li]^+[B(C_6F_5)_4]^-$ (13.7 mg, 0.02 mmol, 0.1 equiv). To this was added trifluorotoluene (2 mL), and the silyl ketene acetal **120a** (130 mg, 0.60 mmol, 3 equiv). Vinyl tosylate **118c** (63.3 mg, 0.2 mmol, 1.0 equiv) was added and the reaction was allowed to stir at 80 °C in a metal heating block placed on an IKA hot plate for 12 hours. The reaction mixture was removed from the glovebox and diluted with ether containing a drop of triethylamine. This was pushed through a plug of triethylamine treated silica gel in a pipette and concentrated *in vacuo* to give the crude material. The crude material was purified by silica flash chromatography on triethylamine treated silica gel (3.5% diethyl ether in hexanes with 0.5% TEA) to give a colorless oil **122b** (40.5 mg, 70% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (dddd, J = 6.9, 2.8, 1.9, 1.0 Hz, 2H), 6.96 – 6.89 (m, 2H), 4.17 (qd, J = 7.2, 0.7 Hz, 2H), 2.35 (s, 3H), 1.67 (s, 3H), 1.55 – 1.47 (m, 1H), 1.33 (s, 3H), 1.32 – 1.24 (m, 5H), 1.20 (s, 3H), 1.13 – 1.04 (m, 1H), 0.79 (t, J = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 178.5, 139.8, 138.4, 135.4, 130.4, 129.8, 129.6, 128.6, 128.5, 60.5, 49.5, 42.3, 24.4, 24.2, 21.3, 22.0, 18.0, 14.9, 14.4.

FT-IR (neat film NaCl): 2961, 2933, 2872, 1726, 1510, 1456, 1374, 1303, 1216, 1138, 1039, 816 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{19}H_{29}O_2$ 289.2162; Found 289.2170.



methyl 2-benzyl-3-(4-methoxyphenyl)-2,4-dimethylpent-3-enoate (122c)

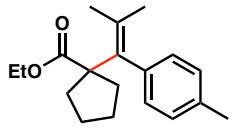
Following General Procedure 1: To an oven dried dram vial with a magnetic stir bar was added $[Li]^+[B(C_6F_5)_4]^-$ (13.7 mg, 0.02 mmol, 0.1 equiv). To this was added trifluorotoluene (2 mL), and the silyl ketene acetal **120b** (150 mg, 0.60 mmol, 3 equiv). Vinyl tosylate **121** (66.5 mg, 0.2 mmol, 1.0 equiv) was added and the reaction was allowed to stir at 80 °C in a metal heating block placed on an IKA hot plate for 12 hours. The reaction mixture was removed from the glovebox and diluted with ether containing a drop of triethylamine. This was pushed through a plug of triethylamine treated silica gel in a pipette and concentrated *in vacuo* to give the crude material. The crude material was purified by silica flash chromatography on triethylamine treated silica gel (4% ethyl acetate in hexanes with 0.5% TEA) to give a colorless oil **122c** (47.0 mg, 69% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.19 (m, 3H), 7.06 – 7.02 (m, 2H), 6.97 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.81 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.66 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.21 (dd, *J* = 8.4, 2.2 Hz, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 2.92 (d, *J* = 13.1 Hz, 1H), 2.83 (d, *J* = 13.2 Hz, 1H), 1.71 (s, 3H), 1.38 (s, 3H), 1.14 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 178.5, 157.7, 138.0, 136.7, 134.9, 131.8, 131.0, 130.8, 130.3, 127.8, 126.5, 113.3, 112.9, 55.2, 52.0, 50.8, 45.1, 24.9, 24.2, 21.0.

FT-IR (neat film NaCl): 3085, 3029, 2993, 2934, 2836, 1726, 1606, 1507, 1454, 1372, 1284, 1242, 1202, 1175, 1103, 1035, 909, 849, 829, 743, 701, 598, 548 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{22}H_{27}O_3$ 339.1955; Found 339.1960.



ethyl 1-(2-methyl-1-(*p*-tolyl)prop-1-en-1-yl)cyclopentane-1-carboxylate (122d)

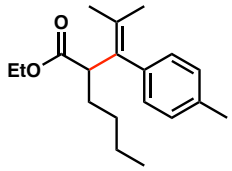
Following General Procedure 1: To an oven dried dram vial with a magnetic stir bar was added $[Li]^+[B(C_6F_5)_4]^-$ (13.7 mg, 0.02 mmol, 0.1 equiv). To this was added trifluorotoluene (2 mL), and the silyl ketene acetal **120c** (130 mg, 0.60 mmol, 3 equiv). Vinyl tosylate **118c** (63.3 mg, 0.2 mmol, 1.0 equiv) was added and the reaction was allowed to stir at 80 °C in a metal heating block placed on an IKA hot plate for 12 hours. The reaction mixture was removed from the glovebox and diluted with ether containing a drop of triethylamine. This was pushed through a plug of triethylamine treated silica gel in a pipette and concentrated *in vacuo* to give the crude material. The crude material was purified by silica flash chromatography on triethylamine treated silica gel (3% diethyl ether in hexanes with 0.5% TEA) to give a colorless oil **122d** (23.0 mg, 40% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 – 7.06 (m, 2H), 6.98 (d, J = 8.0 Hz, 2H), 4.18 (q, J = 7.1 Hz, 2H), 2.35 (s, 3H), 2.22 – 2.14 (m, 2H), 1.72 (s, 3H), 1.53 – 1.48 (m, 4H), 1.37 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 178.1, 140.4, 138.9, 135.4, 131.1, 129.4, 128.6, 60.7, 57.9, 38.2, 24.5, 23.9, 21.4, 21.3, 14.4.

FT-IR (neat film NaCl): 2954, 2871, 1722, 1509, 1450, 1384, 1365, 1321, 1230, 1175, 1160, 1105, 1031, 860,. 814, 585, 533 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{19}H_{27}O_2$ 287.2006; Found 287.2003.



ethyl 2-(2-methyl-1-(*p*-tolyl)prop-1-en-1-yl)hexanoate (122e)

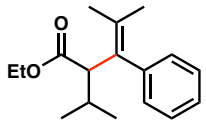
Following General Procedure 1: To an oven dried dram vial with a magnetic stir bar was added $[Li]^+[B(C_6F_5)_4]^-$ (13.7 mg, 0.02 mmol, 0.1 equiv). To this was added trifluorotoluene (2 mL), and the silyl ketene acetal **120d** (130 mg, 0.60 mmol, 3 equiv). Vinyl tosylate **118c** (63.3 mg, 0.2 mmol, 1.0 equiv) was added and the reaction was allowed to stir at 80 °C in a metal heating block placed on an IKA hot plate for 12 hours. The reaction mixture was removed from the glovebox and diluted with ether containing a drop of triethylamine. This was pushed through a plug of triethylamine treated silica gel in a pipette and concentrated *in vacuo* to give the crude material. The crude material was purified by silica flash chromatography on triethylamine treated silica gel (1% ethyl acetate in hexanes with 0.5% TEA) to give a colorless oil **122e** (43.0 mg, 75% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 – 7.01 (m, 2H), 6.95 – 6.72 (m, 2H), 4.07 (qd, J = 7.1, 1.5 Hz, 2H), 3.65 (t, J = 7.4 Hz, 1H), 2.32 (s, 3H), 1.88 (s, 3H), 1.72 – 1.63 (m, 1H), 1.48 (s, 3H), 1.42 – 1.33 (m, 1H), 1.31 – 1.24 (m, 4H), 1.21 (t, J = 7.1 Hz, 3H), 0.89 – 0.83 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 137.8, 135.8, 132.8, 131.8, 129.5, 128.6, 60.3, 48.6, 30.0, 29.97, 22.9, 22.8, 21.3, 20.5, 14.4, 14.2.

FT-IR (neat film NaCl): 2956, 2927, 2860, 1732, 1510, 1446, 1367, 1217, 1175, 1128, 1112, 1032, 817, 728, 568 cm^{-1}.

HR-MS (ESI) m/z: [M+Na]+ Calculated for $C_{19}H_{28}NaO_2$ 311.1982; Found 311.1984.



ethyl 2-isopropyl-4-methyl-3-phenylpent-3-enoate (122f)

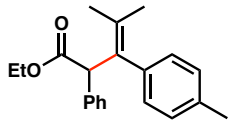
Following General Procedure 1: To an oven dried dram vial with a magnetic stir bar was added $[Li]^+[B(C_6F_5)_4]^-$ (13.7 mg, 0.02 mmol, 0.1 equiv). To this was added trifluorotoluene (2 mL), and the silyl ketene acetal **120e** (121 mg, 0.60 mmol, 3 equiv). Vinyl tosylate **118b** (60.5 mg, 0.2 mmol, 1.0 equiv) was added and the reaction was allowed to stir at 80 °C in a metal heating block placed on an IKA hot plate for 12 hours. The reaction mixture was removed from the glovebox and diluted with ether containing a drop of triethylamine. This was pushed through a plug of triethylamine treated silica gel in a pipette and concentrated *in vacuo* to give the crude material. The crude material was purified by silica flash chromatography on triethylamine treated silica gel (3% diethyl ether in hexanes with 0.5% TEA) to give a colorless oil **122f** (30.0 mg, 58% yield).

^{1}H NMR (400 MHz, C_6D_6) δ 7.25 – 7.18 (m, 4H), 7.13 – 7.08 (m, 1H), 3.95 (q, *J* = 7.1 Hz, 2H), 3.51 (d, *J* = 11.0 Hz, 1H), 2.20 (dp, *J* = 10.9, 6.5 Hz, 1H), 1.83 (s, 3H), 1.47 (s, 3H), 1.01 (d, *J* = 6.4 Hz, 3H), 0.93 (t, *J* = 7.1 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 141.1, 133.5, 132.0, 129.8, 127.8, 126.4, 77.4, 60.1, 57.1, 29.9, 28.1, 23.2, 21.5, 20.9, 20.6, 14.3.

FT-IR (neat film NaCl): 2959, 2927, 2870, 1735, 1366, 1278, 1234, 1178, 1120, 1033, 702 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{17}H_{25}O_2$ 261.1849; Found 261.1845.



ethyl 4-methyl-2-phenyl-3-(*p*-tolyl)pent-3-enoate (122g)

Following General Procedure 1: To an oven dried dram vial with a magnetic stir bar was added $[Li]^+[B(C_6F_5)_4]^-$ (13.7 mg, 0.02 mmol, 0.1 equiv). To this was added trifluorotoluene (2 mL), and the silyl ketene acetal **120f** (142 mg, 0.60 mmol, 3 equiv). Vinyl tosylate **118c** (63.3 mg, 0.2 mmol, 1.0 equiv) was added and the reaction was allowed to stir at 80 °C in a metal heating block placed on an IKA hot plate for 12 hours. The reaction mixture was removed from the glovebox and diluted with ether containing a drop of triethylamine. This was pushed through a plug of triethylamine treated silica gel in a pipette and concentrated *in vacuo* to give the crude material. The crude material was purified by silica flash chromatography on triethylamine treated silica gel (3% diethyl ether in hexanes with 0.5% TEA) to give a colorless oil **122g** (17.0 mg, 27% yield).

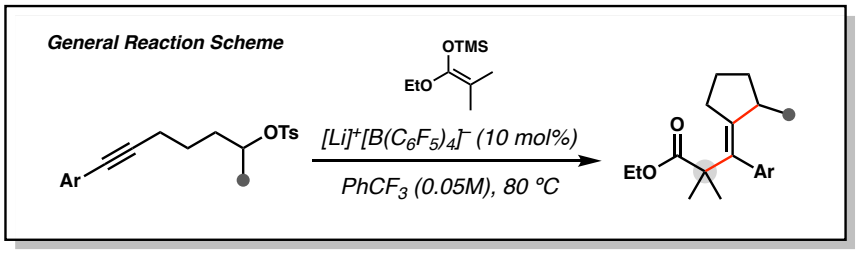
^{1}H NMR (400 MHz, $CDCl_3$) 7.25 – 7.17 (m, 3H), 7.17 – 7.11 (m, 2H), 7.01 – 6.96 (m, 2H), 6.84 – 6.71 (m, 2H), 5.05 (s, 1H), 4.08 (q, J = 7.1 Hz, 2H), 2.28 (s, 3H), 1.88 (s, 3H), 1.56 (s, 3H), 1.17 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 138.2, 137.8, 135.7, 132.8, 132.3, 129.9, 129.4, 128.3, 128.0, 126.7, 60.8, 55.2, 23.0, 21.2, 20.9, 14.2.

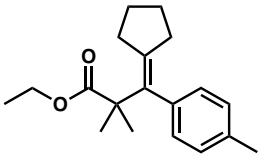
FT-IR (neat film NaCl): 2959, 2927, 2870, 1735, 1366, 1278, 1234, 1178, 1120, 1033, 702 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{21}H_{25}O_2$ 309.1849; Found 309.1855.

2.7.6 Cyclization Cascade Reactions



General Procedure 2: All reactions were conducted in a well-maintained glove box (O_2, H_2O <0.5 ppm) on 0.2 mmol scale unless otherwise noted. To an oven dried dram vial with a magnetic stir bar was added $[Li]^+[B(C_6F_5)_4]^-$ (13.7 mg, 0.02 mmol, 0.1 equiv). To this was added trifluorotoluene (4 mL), and the corresponding silyl ketene acetal (3 equiv). Substrate (0.2 mmol, 1.0 equiv) was added and the reaction was allowed to stir at 80 °C in a metal heating block placed on an IKA hot plate for 24 hours. The reactions were monitored by TLC, typically using 10% diethyl ether in hexanes for the mobile phase (α-vinylation products are typically higher in R_f than the starting tosylate). Upon completion of reaction, the reaction mixture was removed from the glovebox and diluted with ether containing a drop of triethylamine. This was pushed through a plug of triethylamine treated silica gel in a pipette. The reaction mixture was concentrated in vacuo to give the crude material, which was purified by silica flash chromatography on triethylamine treated silica gel (typically 1–2% diethyl ether in hexanes with 0.1% triethylamine) and then dried on high vacuum to obtain material that is pure by ^1H NMR.



ethyl 3-cyclopentylidene-2,2-dimethyl-3-(*p*-tolyl)propanoate (131a)

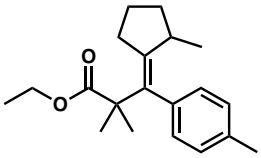
Following General Procedure 2: To an oven dried dram vial with a magnetic stir bar was added $[Li]^+[B(C_6F_5)_4]^-$ (13.7 mg, 0.02 mmol, 0.1 equiv). To this was added trifluorotoluene (4 mL), and the silyl ketene acetal **116b** (113.0 mg, 3 equiv, .6 mmol). Alkyl tosylate **130a** (68.5 mg, 1.0 equiv, 0.2 mmol) was added and the reaction was allowed to stir at 80 °C in a metal heating block placed on an IKA hot plate for 24 hours. The reaction mixture was removed from the glovebox and diluted with ether containing a drop of triethylamine. This was pushed through a plug of triethylamine treated silica gel in a pipette and concentrated *in vacuo* to give the crude material. The crude material was purified by silica flash chromatography on triethylamine treated silica gel (2% diethyl ether in hexanes with 0.1% TEA) to give a colorless oil **131a** (31.9 mg, 56% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 7.08 (m, 2H), 7.00 – 6.92 (m, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.34 (s, 3H), 2.16 (tt, *J* = 7.1, 1.4 Hz, 2H), 1.85 (tt, *J* = 7.4, 1.2 Hz, 2H), 1.69 – 1.57 (m, 2H), 1.51 – 1.40 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.18 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 178.5, 141.8, 140.0, 135.6, 135.5, 129.0, 128.8, 60.6, 46.5, 34.0, 30.4, 27.5, 26.6, 25.8, 21.3, 14.3.

FT-IR (neat film NaCl): 2971, 2953, 2867, 1726, 1509, 1466, 1382, 1248, 1134, 1030, 806 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{19}H_{27}O_2^+$: 287.2006 ; Found 287.2013.



ethyl 2,2-dimethyl-3-(2-methylcyclopentylidene)-3-(*p*-tolyl)propanoate (131b)

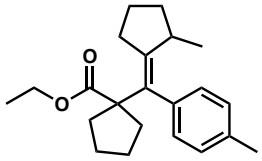
Following General Procedure 2: To an oven dried dram vial with a magnetic stir bar was added $[Li]^+[B(C_6F_5)_4]^-$ (13.7 mg, 0.02 mmol, 0.1 equiv). To this was added trifluorotoluene (4 mL), and the silyl ketene acetal **116b** (113.0 mg, 3 equiv, .6 mmol). Alkyl tosylate **130b** (71.3 mg, 0.2 mmol, 1.0 equiv) was added and the reaction was allowed to stir at 80 °C in a metal heating block placed on an IKA hot plate for 24 hours. The reaction mixture was removed from the glovebox and diluted with ether containing a drop of triethylamine. This was pushed through a plug of triethylamine treated silica gel in a pipette and concentrated *in vacuo* to give the crude material. The crude material was purified by silica flash chromatography on triethylamine treated silica gel (1% → 2% diethyl ether in hexanes with 0.1% TEA) to give a colorless oil **131b** (42.1 mg, 70% yield). *The olefin isomer (E) was assigned on the basis of NOESY NMR.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 – 7.06 (m, 2H), 6.98 (ddd, *J* = 11.9, 7.4, 1.5 Hz, 2H), 4.24 – 4.08 (m, 2H), 2.35 (s, 3H), 2.32 (s, 1H), 2.25 – 2.09 (m, 2H), 1.79 – 1.68 (m, 1H), 1.67 – 1.54 (m, 2H), 1.34 – 1.20 (m, 4H), 1.17 (s, 3H), 1.12 (s, 3H), 0.66 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 178.7, 146.6, 138.9, 135.8, 135.5, 130.2, 129.2, 128.8, 128.0, 60.5, 46.5, 38.4, 33.8, 29.0, 27.0, 26.3, 24.1, 21.3, 20.2, 14.3.

FT-IR (neat film NaCl): 2973, 2954, 2867, 1728, 1509, 1467, 1382, 1247, 1133, 1030 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{20}H_{29}O_2^+$: 301.2162 ; Found 301.2170.



Ethyl (*E*)-1-((2-methylcyclopentylidene)(*p*-tolyl)methyl)cyclopentane-1-carboxylate (131c)

Following General Procedure 2: To an oven dried dram vial with a magnetic stir bar was added $[Li]^+[B(C_6F_5)_4]^-$ (13.7 mg, 0.02 mmol, 0.1 equiv). To this was added trifluorotoluene (4 mL), and the silyl ketene acetal **120c** (128.6 mg, 3 equiv, 0.6 mmol). Alkyl tosylate **130b** (71.3 mg, 1.0 equiv, 0.2 mmol) was added and the reaction was allowed to stir at 80 °C in a metal heating block placed on an IKA hot plate for 24 hours. The reaction mixture was removed from the glovebox and diluted with ether containing a drop of triethylamine. This was pushed through a plug of triethylamine treated silica gel in a pipette and concentrated *in vacuo* to give the crude material. The crude material was purified by silica flash chromatography on triethylamine treated silica gel (1% → 2% diethyl ether in hexanes with 0.1% TEA) to give a colorless oil **131c** (27.1 mg, 42% yield). The olefin isomer (E) was assigned on the basis of NOESY NMR. Trace amounts of a second compound appear in NMR which may correspond to the Z isomer, though integration of its integral suggests <5%, and isolation of sufficient quantities of this minor product could not be achieved to definitively assign it as the Z isomer.

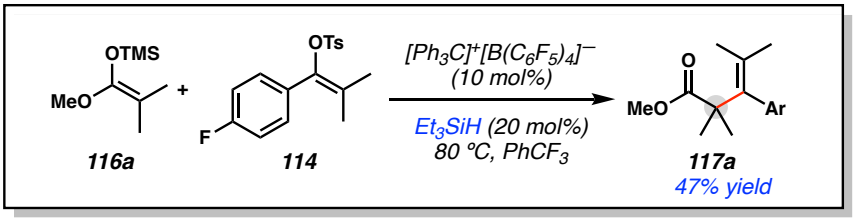
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 – 7.03 (m, 3H), 7.02 – 6.95 (m, 1H), 4.17 (qq, *J* = 10.8, 7.1 Hz, 2H), 2.39 – 2.19 (m, 7H), 2.19 – 2.07 (m, 1H), 1.79 – 1.39 (m, 9H), 1.33 – 1.19 (m, 4H), 0.64 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 147.8, 139.7, 135.7, 135.4, 130.0, 129.2, 128.7, 128.0, 60.0, 58.5, 38.3, 37.9, 36.5, 33.9, 29.8, 24.2, 23.9, 21.3, 19.9, 14.4.

FT-IR (neat film NaCl): 2953, 2869, 1723, 1508, 1450, 1229, 1175, 1157, 1106, 1031, 823 cm^{-1}.

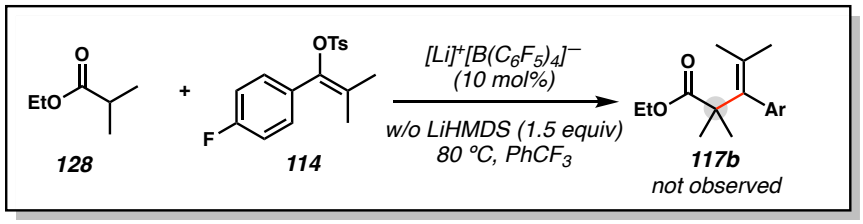
HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{22}H_{31}O_2^+$: 327.2319 ; Found 327.2330.

2.7.7 Mechanistic Studies

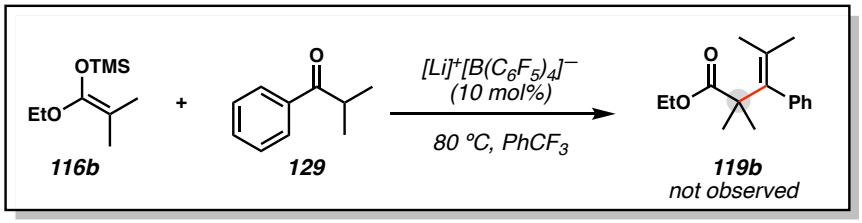


To an oven dried dram vial with a magnetic stir bar was added $[Ph_3C]^+[B(C_6F_5)_4]^-$ (4.6 mg, 0.005 mmol, 0.1 equiv). To this was added trifluorotoluene (0.5 mL), and then triethylsilane (1.60 µL, 0.01 mmol, 0.2 equiv). ((1-methoxy-2-methylprop-1-en-1-yl)oxy)trimethylsilane (**116a**) (26.1 mg, 0.150 mmol, 3 equiv) was added next, and then finally vinyl tosylate **114** (16.0 mg, 0.05 mmol, 1.0 equiv) was added and the reaction was allowed to stir at 80 °C in a metal heating block placed on an IKA hot plate for 12 hours. The reaction mixture was removed from the glovebox and diluted with ether containing a drop of triethylamine. This was pushed through a plug of triethylamine treated silica gel in

a pipette and concentrated *in vacuo* to give the crude material. The 47% yield of **117a** was determined by ^{19}F NMR using C_6F_6 as an internal standard.



To an oven dried dram vial with a magnetic stir bar was added $[Li]^+[B(C_6F_5)_4]^-$ (3.14 mg, 0.005 mmol, 0.1 equiv) and LiHMDS (12.5 mg, 1.5 equiv, 0.075 mmol). To this was added trifluorotoluene (0.5 mL) and ethyl isobutyrate (**128**) (20.1 μL, 3 equiv, 0.150 mmol). Vinyl tosylate **114** (16.0 mg, 0.05 mmol, 1.0 equiv) was added and the reaction was allowed to stir at 80 °C in a metal heating block placed on an IKA hot plate for 12 hours. The reaction mixture was removed from the glovebox and diluted with ether containing a drop of triethylamine. This was pushed through a plug of triethylamine treated silica gel in a pipette and concentrated *in vacuo* to give the crude material, which was determined by TLC and ^1H NMR to give no conversion to the desired product.



To an oven dried dram vial with a magnetic stir bar was added $[Li]^+[B(C_6F_5)_4]^-$ (3.14 mg, 0.005 mmol, 0.1 equiv). To this was added trifluorotoluene (0.5 mL) and silyl ketene acetal

116b (28.3 mg, 3 equiv, 0.150 mmol). Isobutyrophenone **129** (7.5 μL, 0.05 mmol, 1.0 equiv) was added and the reaction was allowed to stir at 80 °C in a metal heating block placed on an IKA hot plate for 12 hours. The reaction mixture was removed from the glovebox and diluted with ether containing a drop of triethylamine. This was pushed through a plug of triethylamine treated silica gel in a pipette and concentrated *in vacuo* to give the crude material, which was determined by TLC and ^{1}H NMR to give no conversion to the desired product.

2.8 NOTES AND REFERENCES

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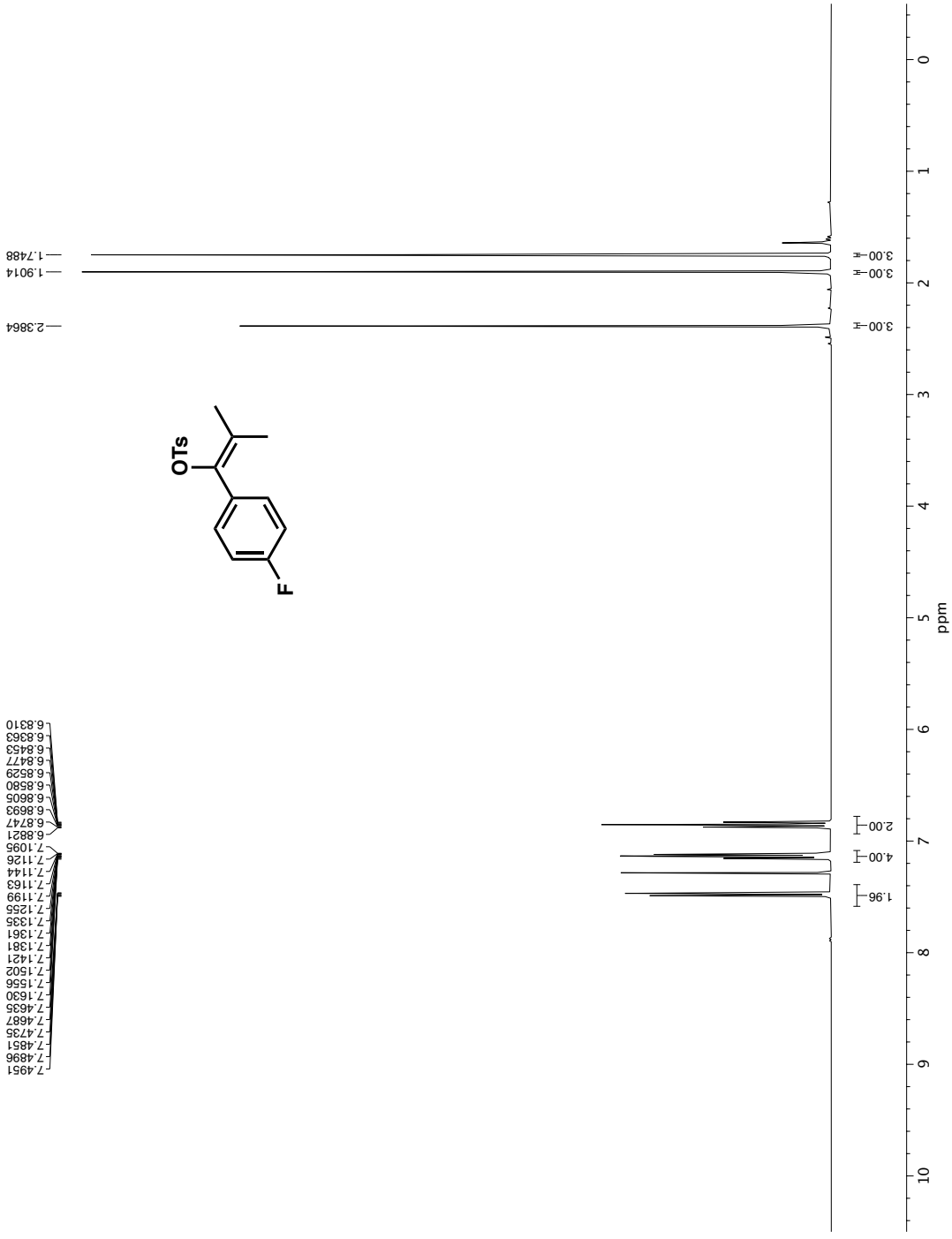
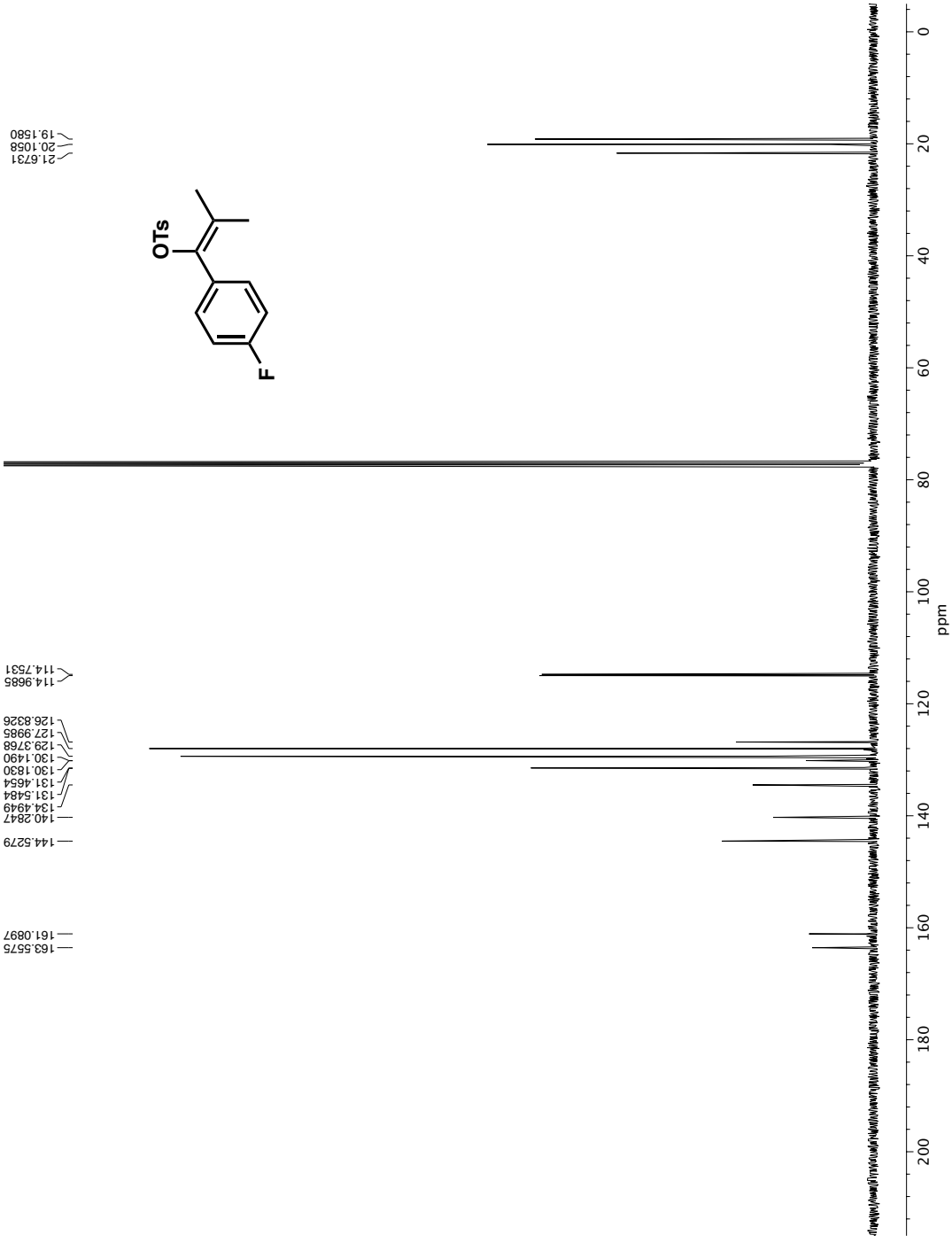
Appendix 1

Spectra Relevant to Chapter 2:

α–Vinylation of Ester Equivalents via Main Group Catalysis for the Construction of Quaternary Centers

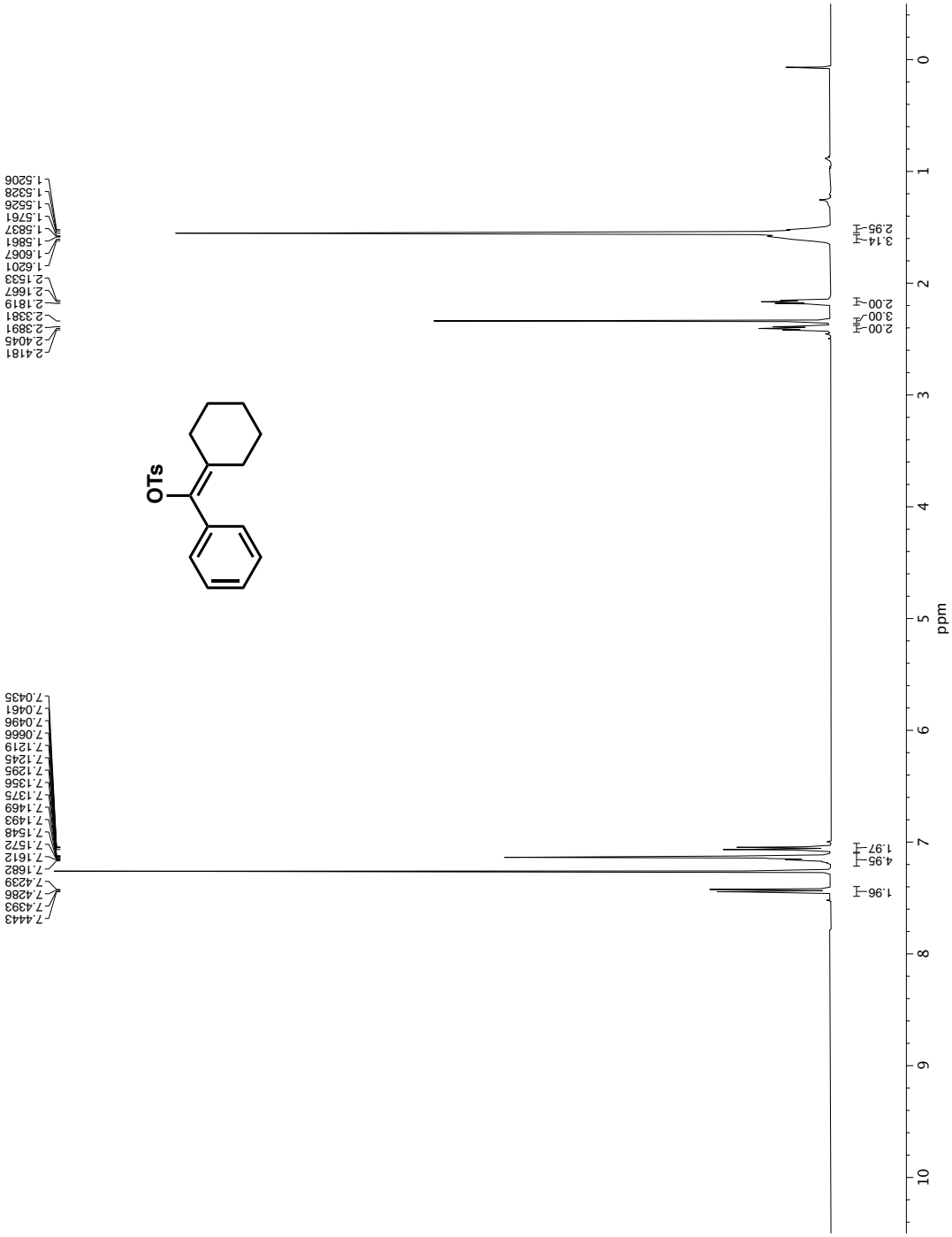


^{1}H NMR (400 MHz, $CDCl_3$) of compound **114**.

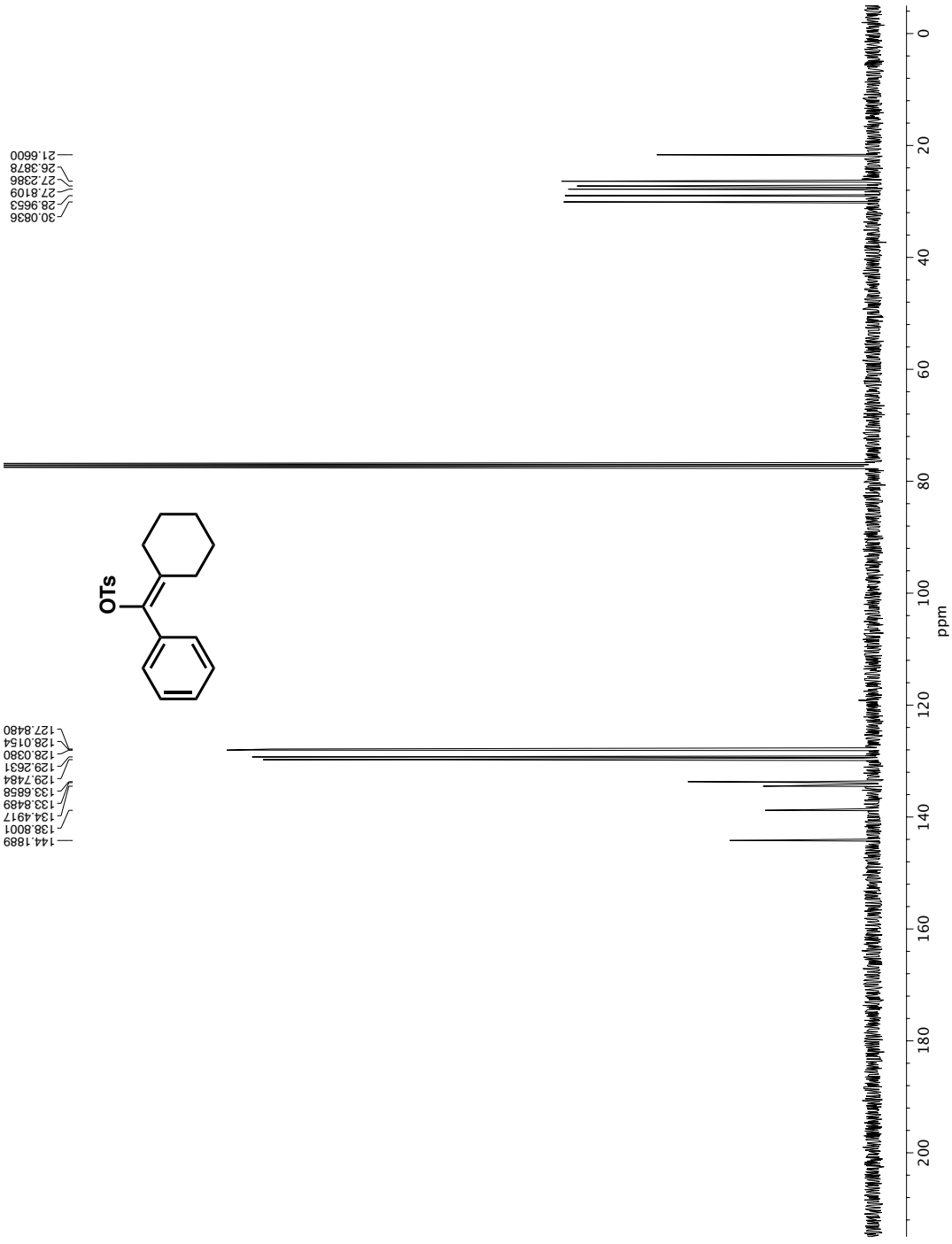


^{13}C NMR (101 MHz, $CDCl_3$) of compound **114**.

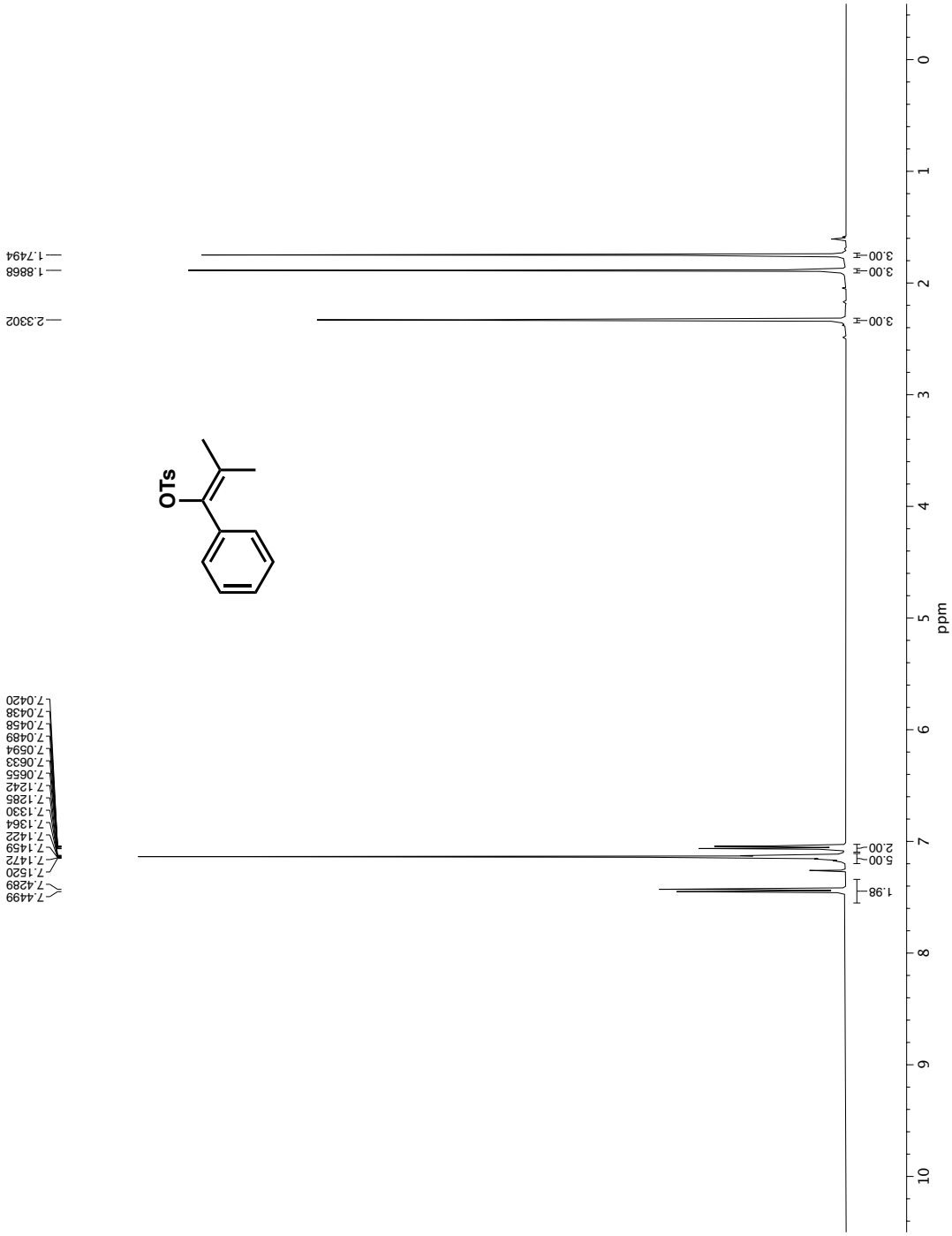
^{19}F NMR (282 MHz, $CDCl_3$) of compound **114**.



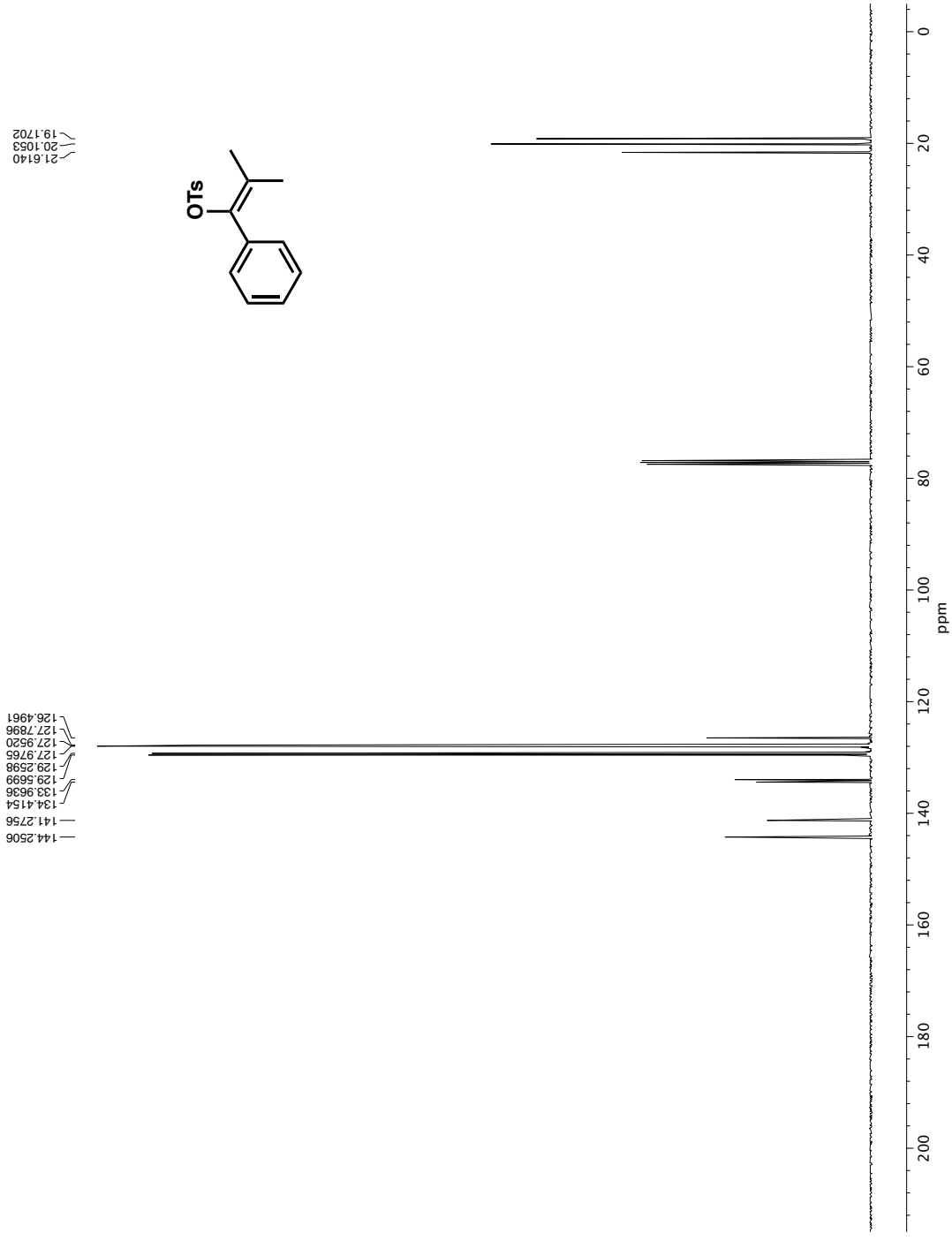
^{1}H NMR (400 MHz, $CDCl_3$) of compound **188a**.



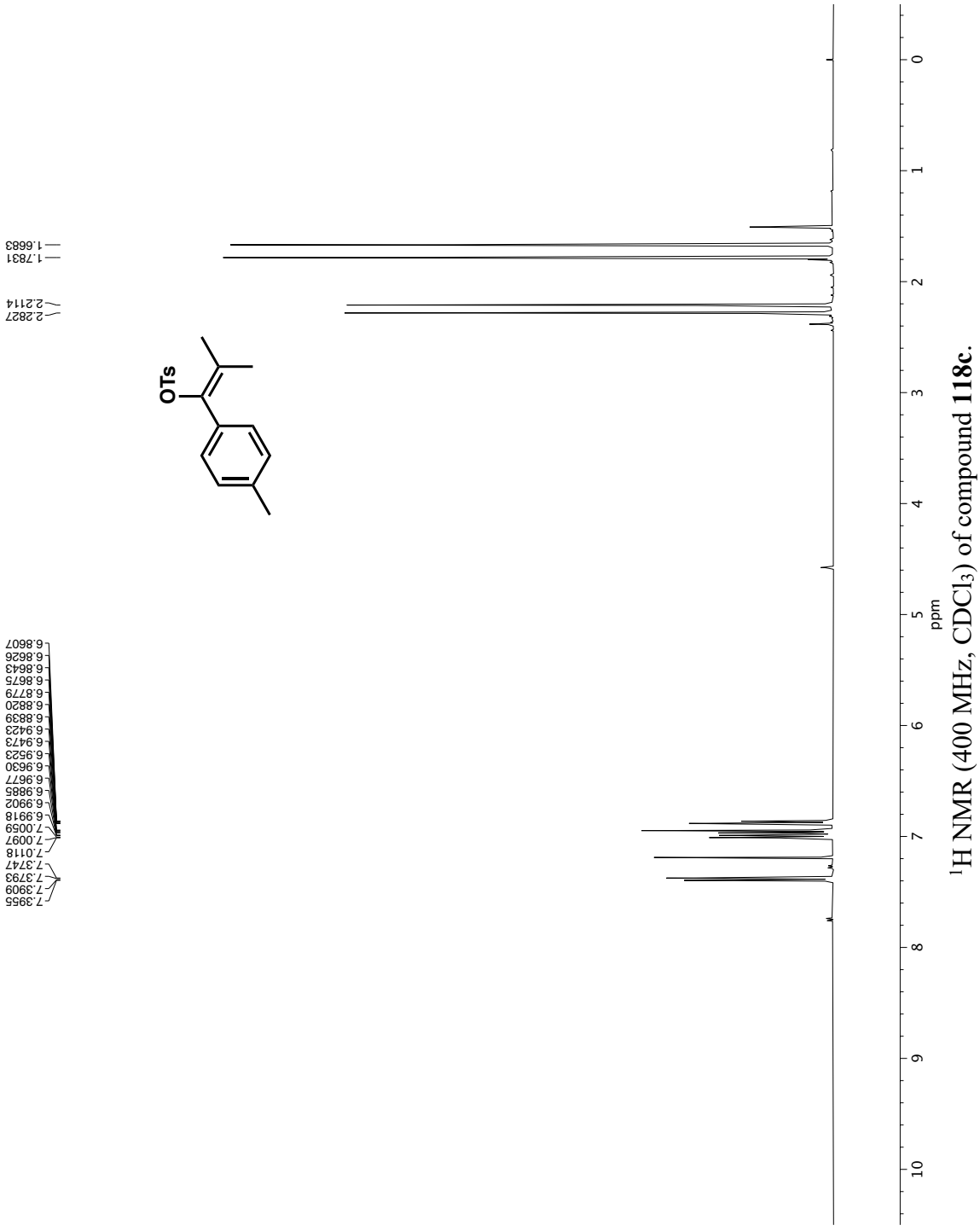
^{13}C NMR (101 MHz, $CDCl_3$) of compound **188a**.



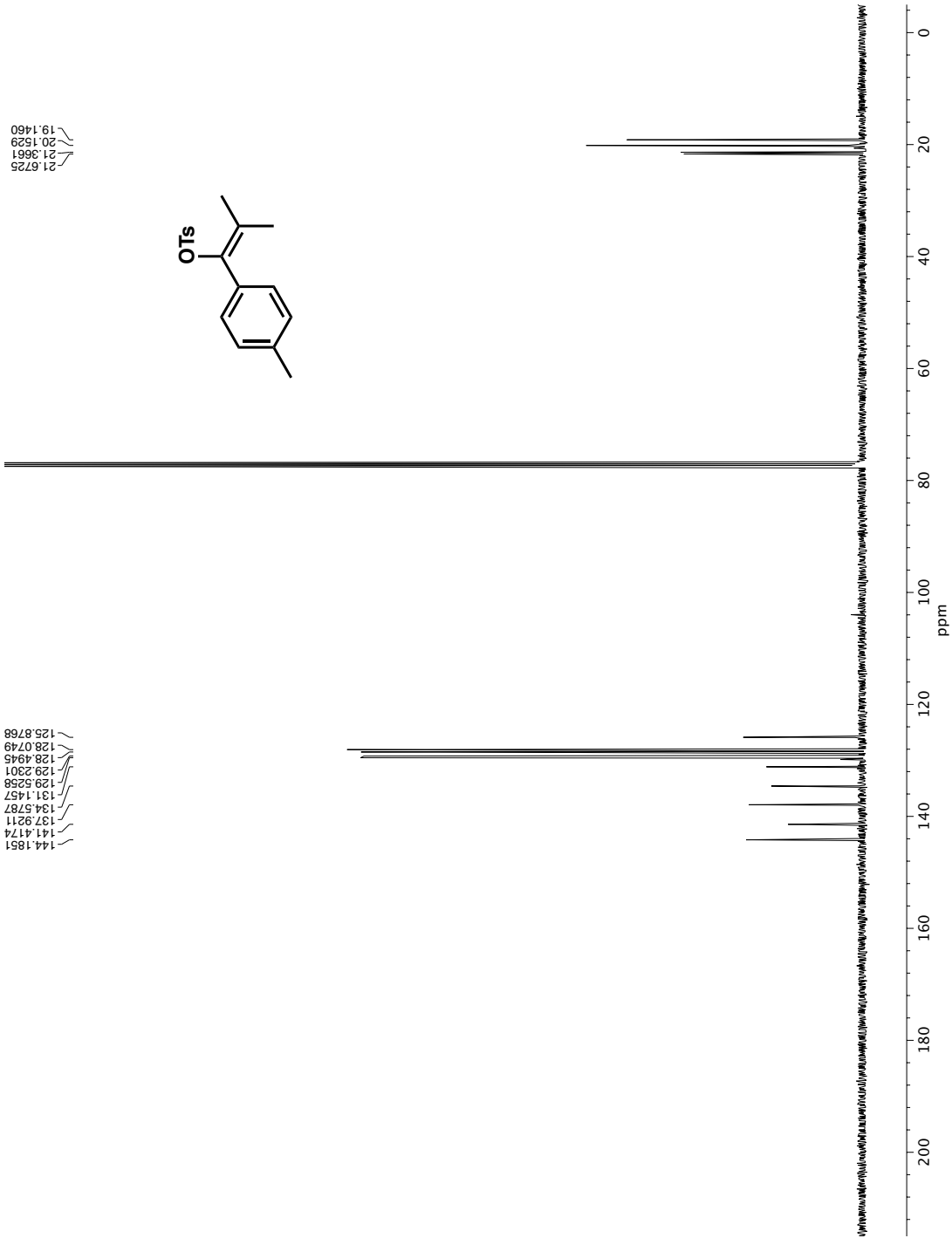
^{1}H NMR (400 MHz, $CDCl_3$) of compound **188b**.



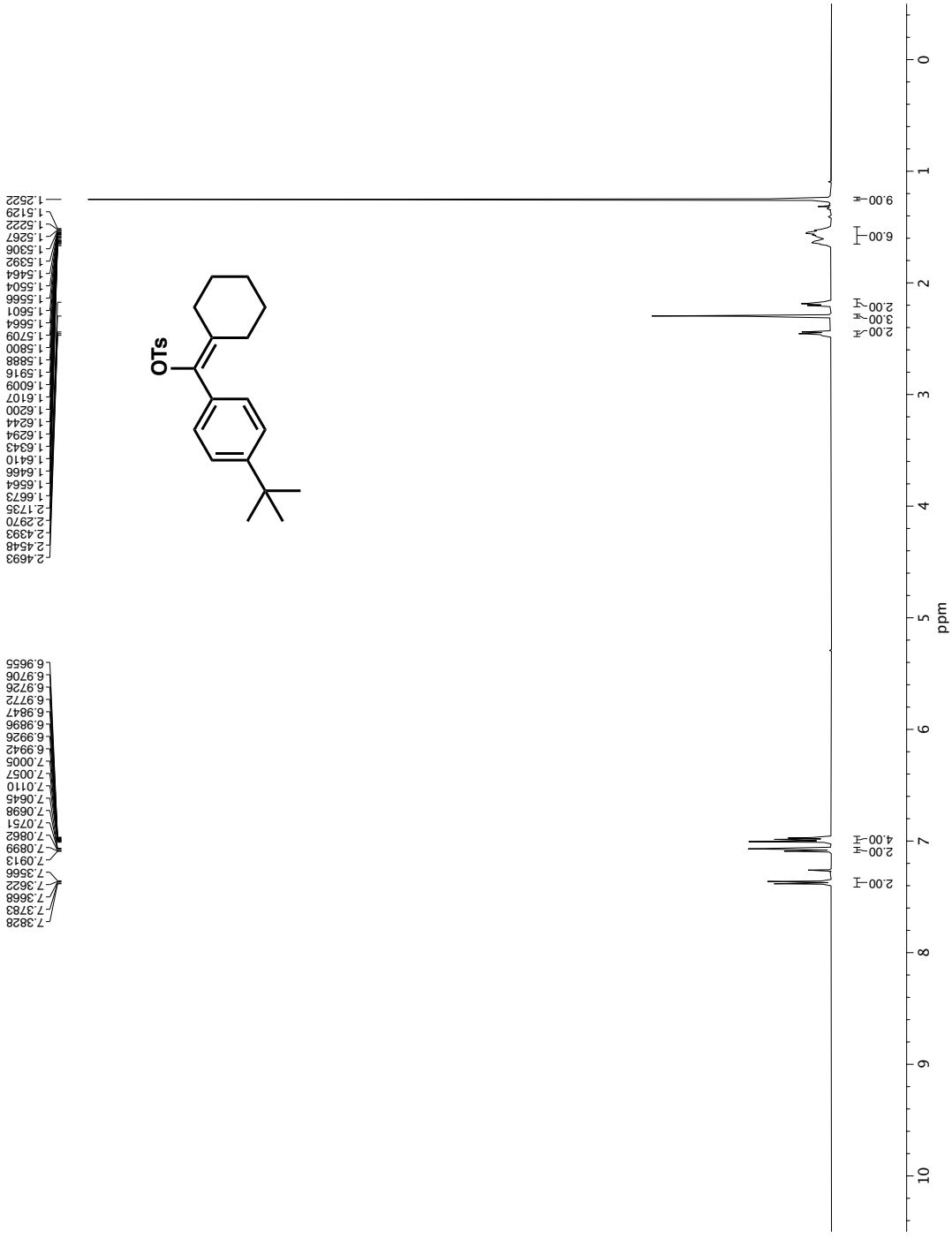
^{13}C NMR (101 MHz, $CDCl_3$) of compound **188b**.



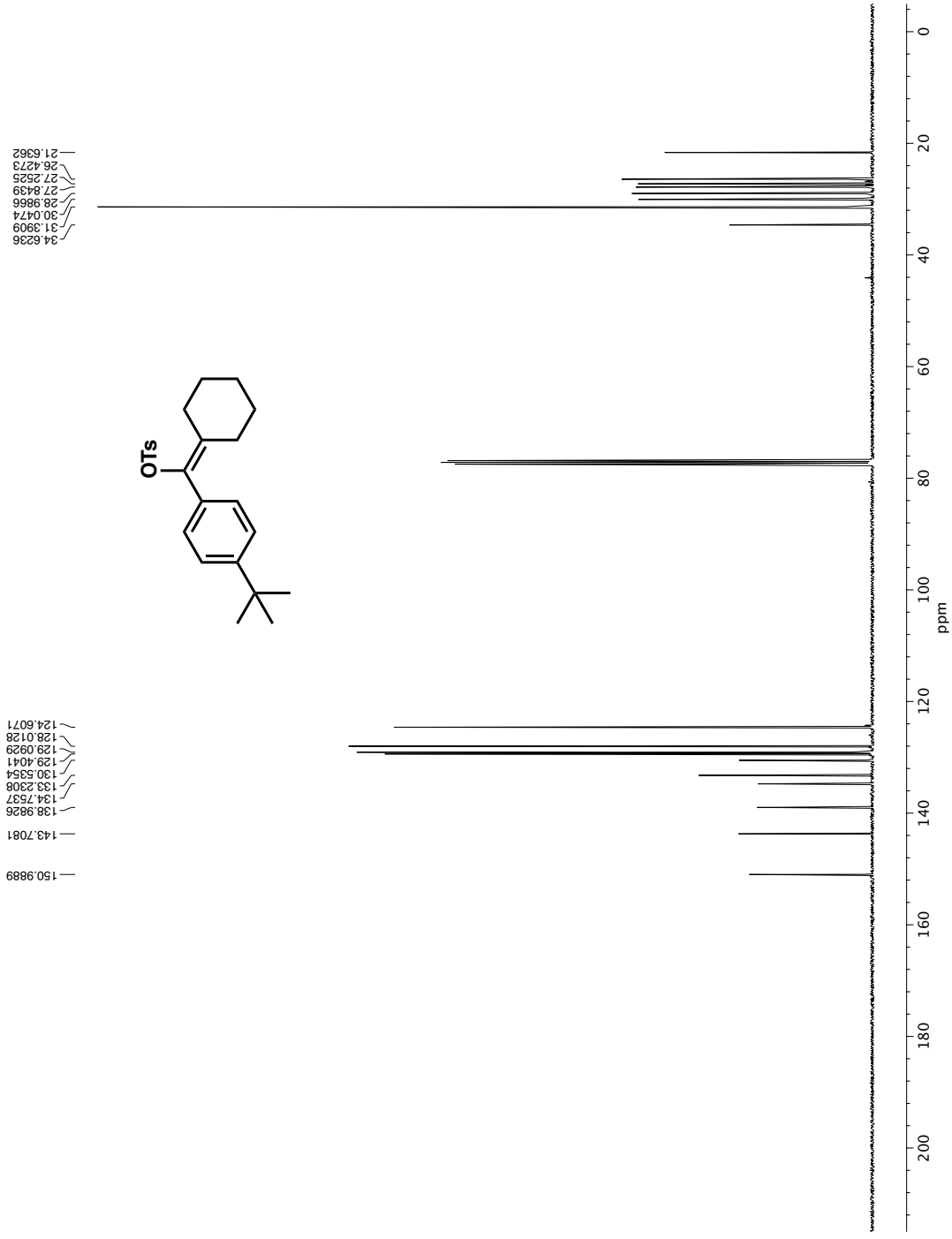
^{1}H NMR (400 MHz, $CDCl_3$) of compound **118c**.



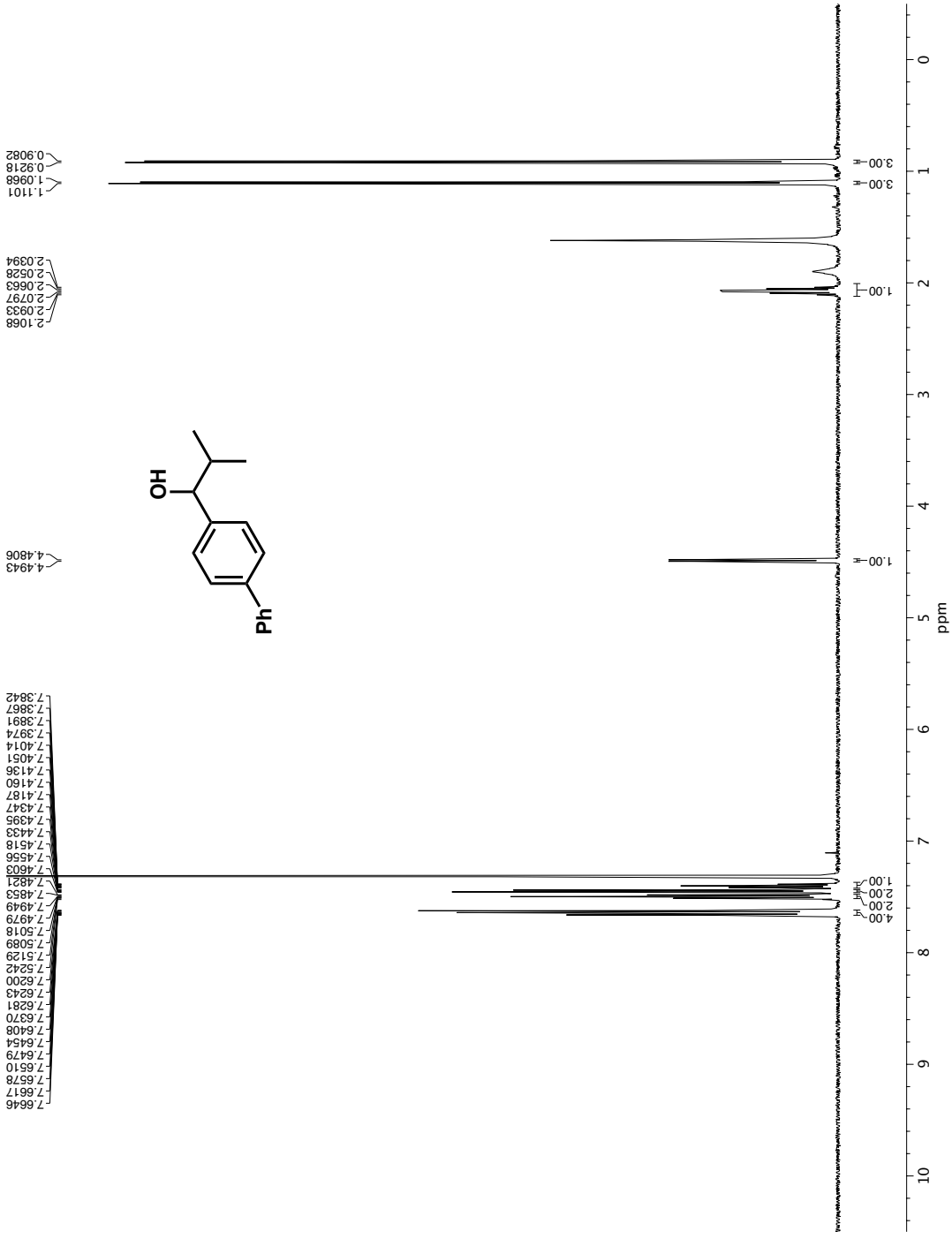
^{13}C NMR (101 MHz, $CDCl_3$) of compound **118c**.



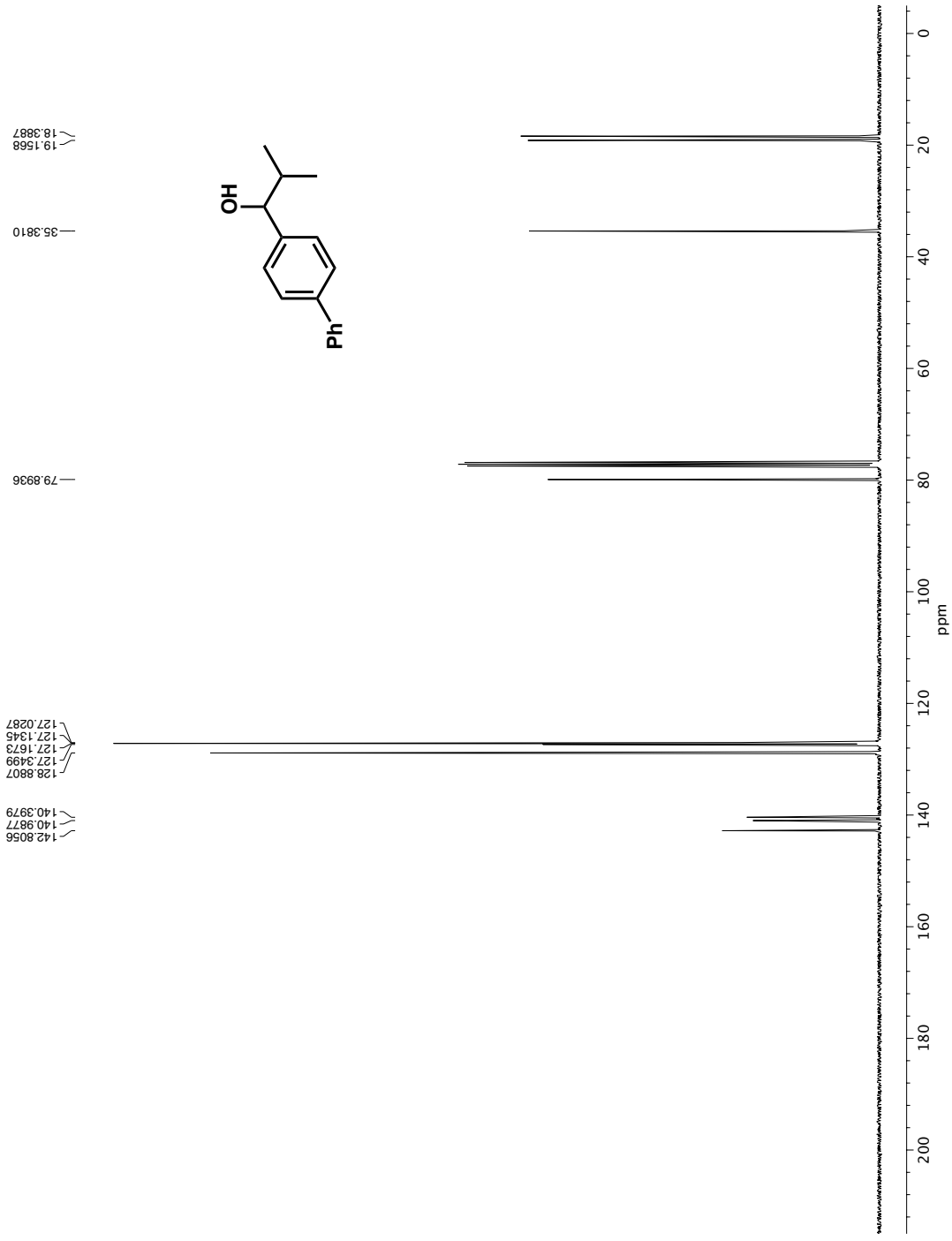
^{1}H NMR (400 MHz, $CDCl_3$) of compound **118d**.



^{13}C NMR (101 MHz, $CDCl_3$) of compound **118d.**



^{1}H NMR (500 MHz, $CDCl_3$) of compound **134**.



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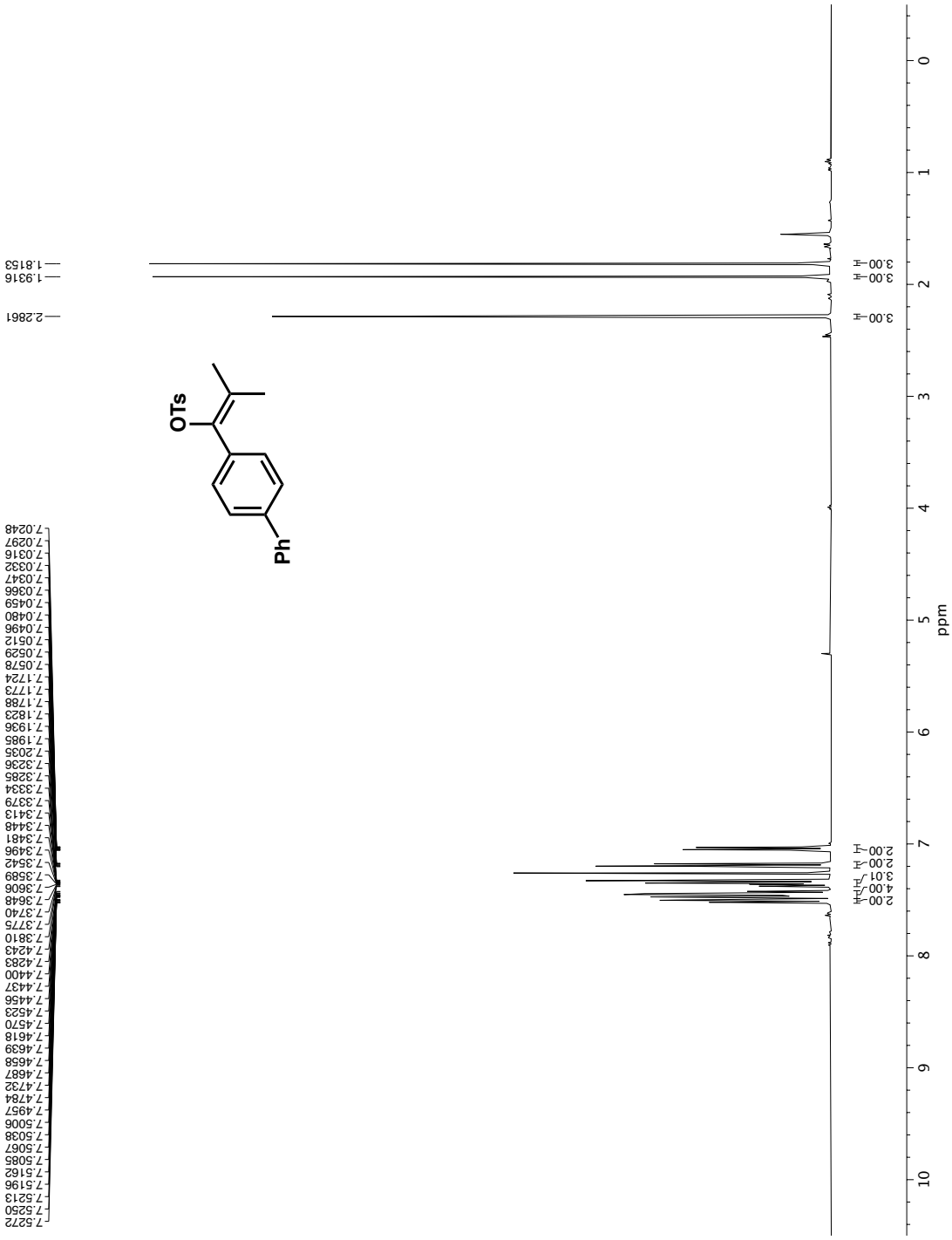
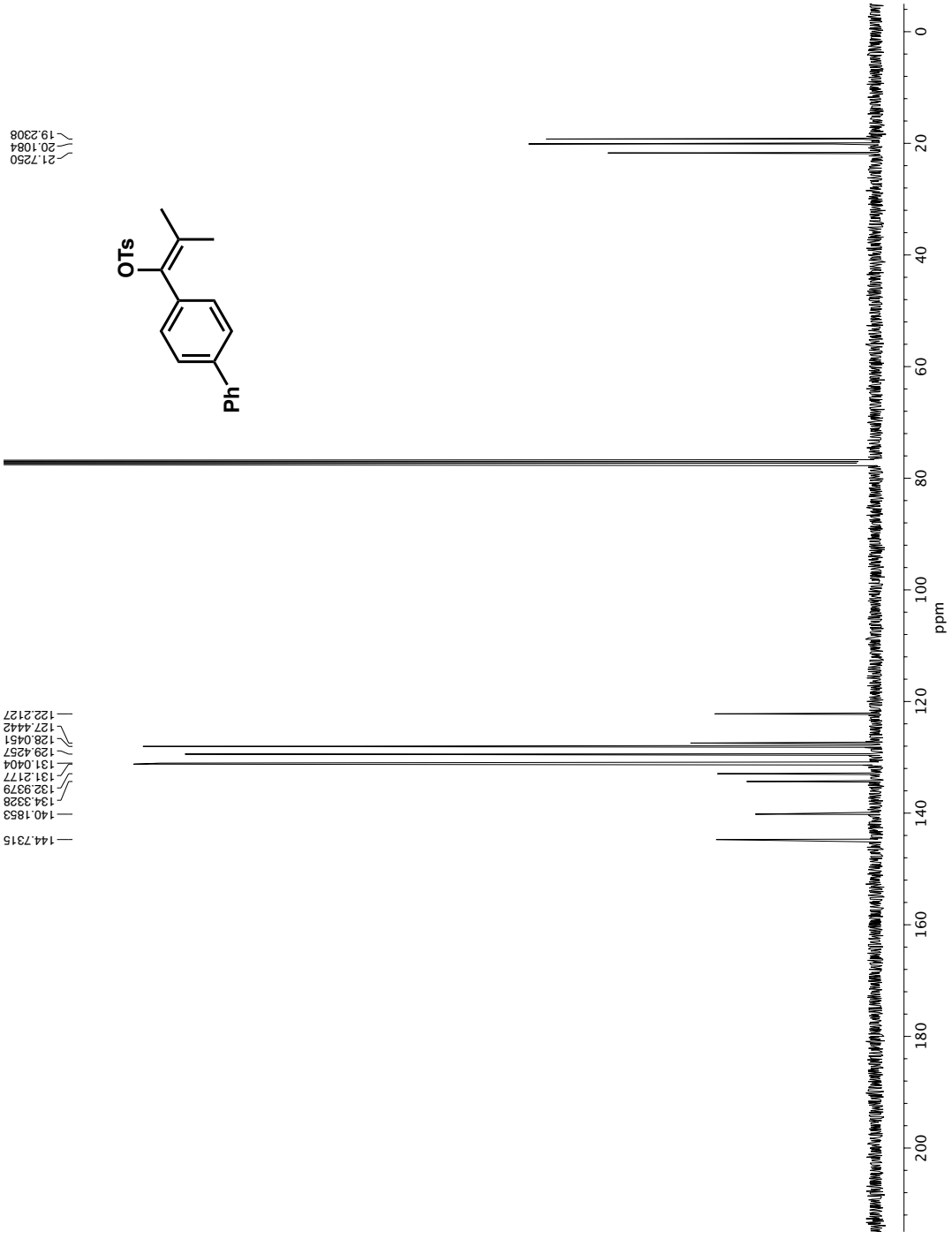


^{1}H NMR (400 MHz, $CDCl_3$) of compound **118e**.



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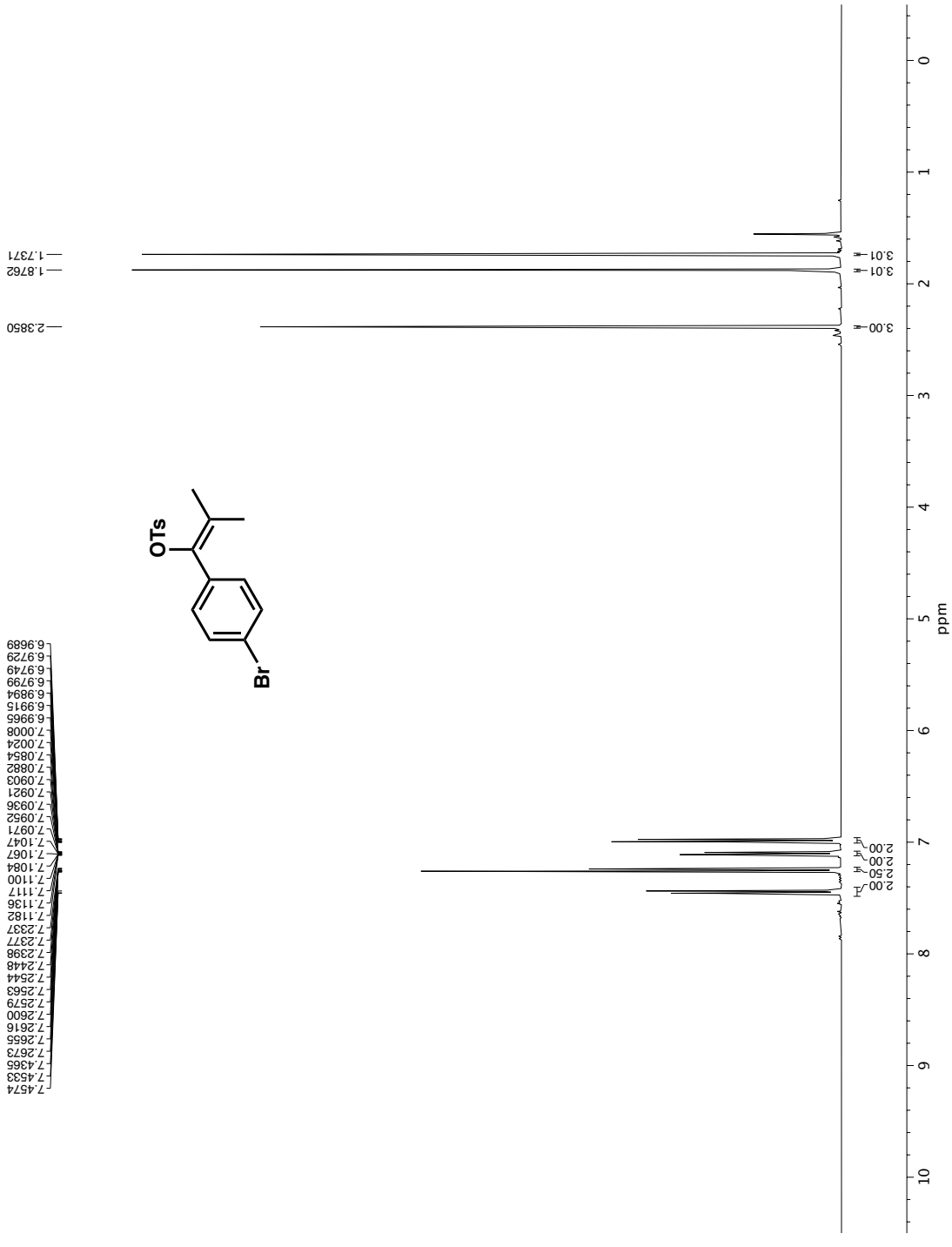
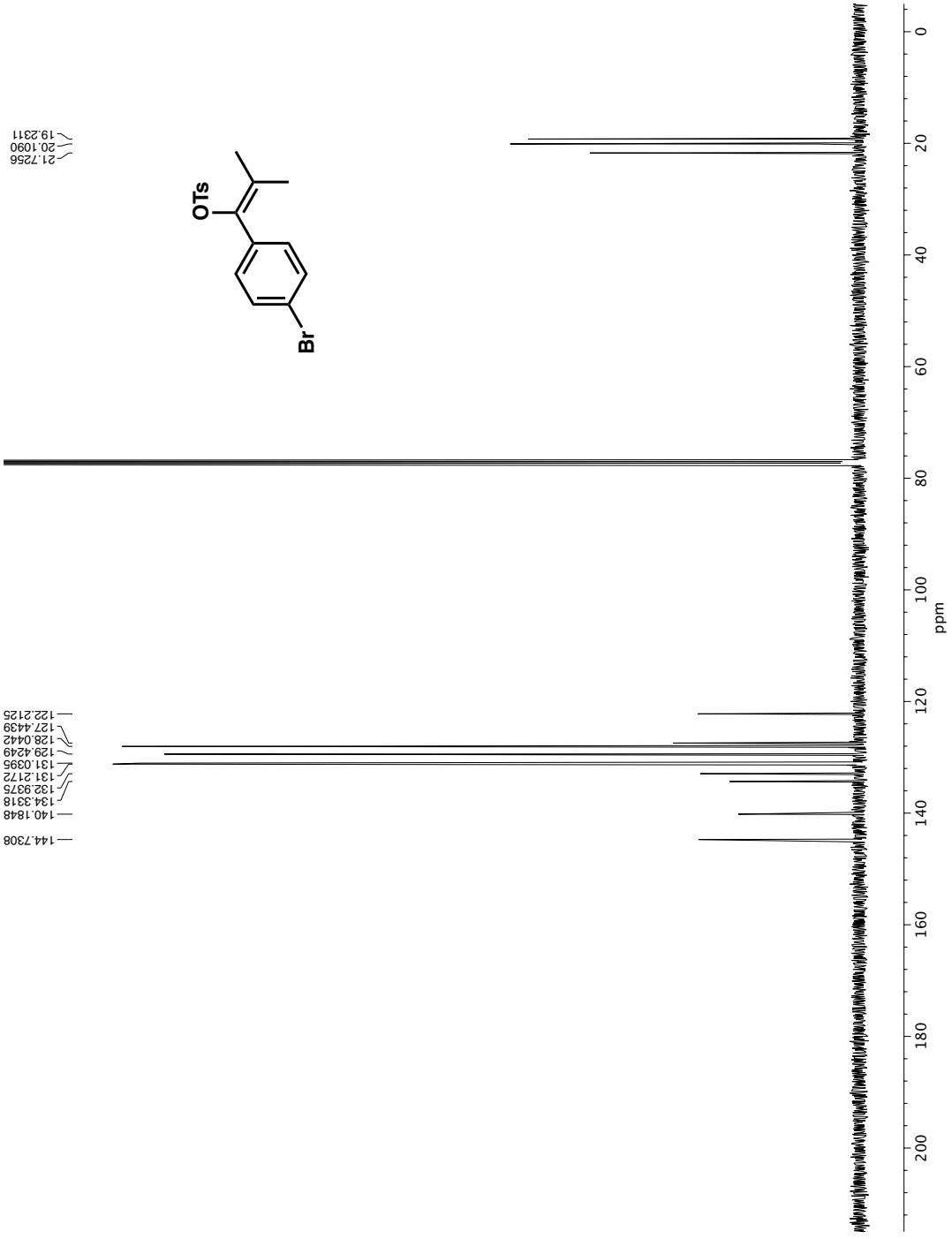
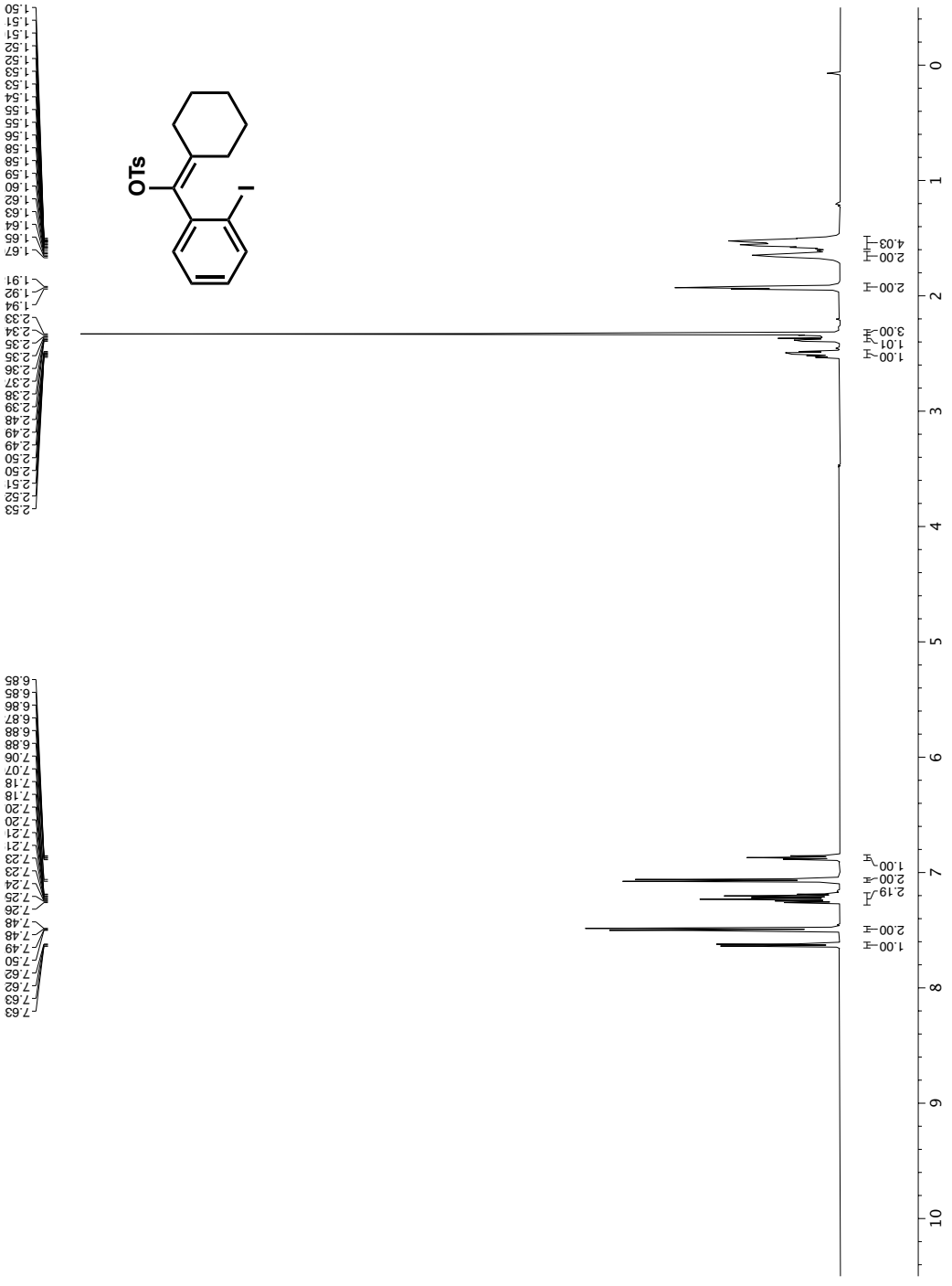


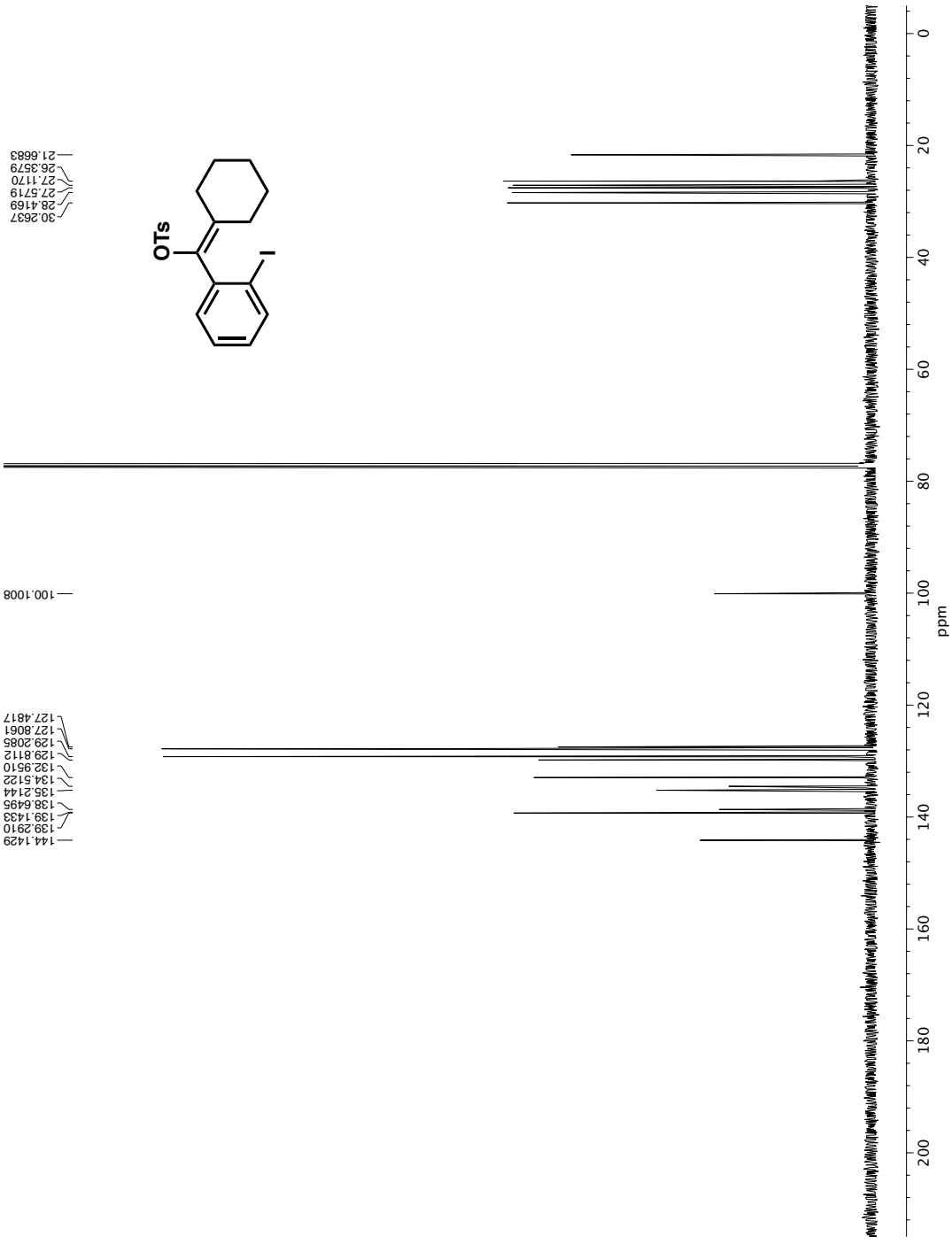
^{1}H NMR (400 MHz, $CDCl_3$) of compound **118f**.



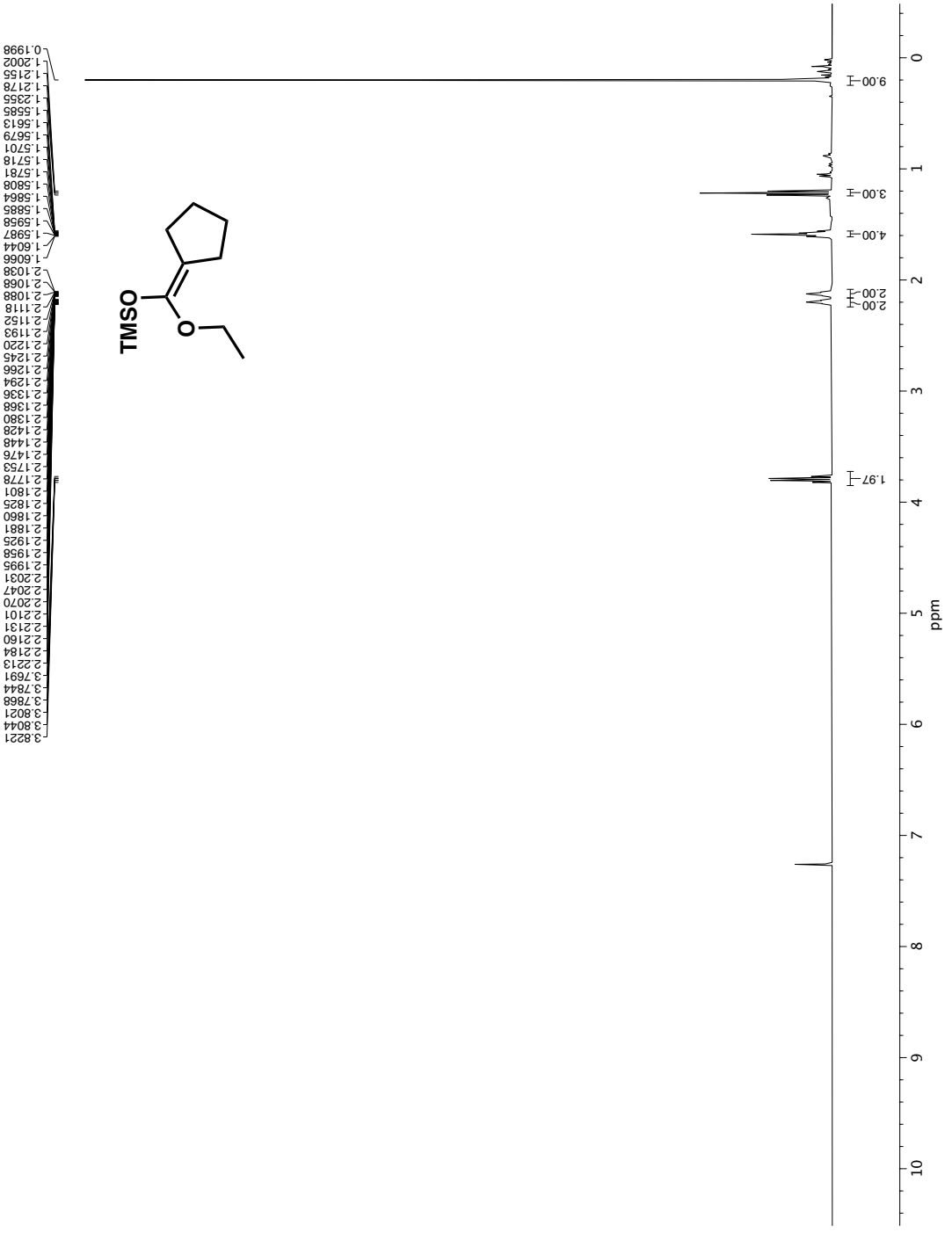
^{13}C NMR (101 MHz, $CDCl_3$) of compound **118f**.



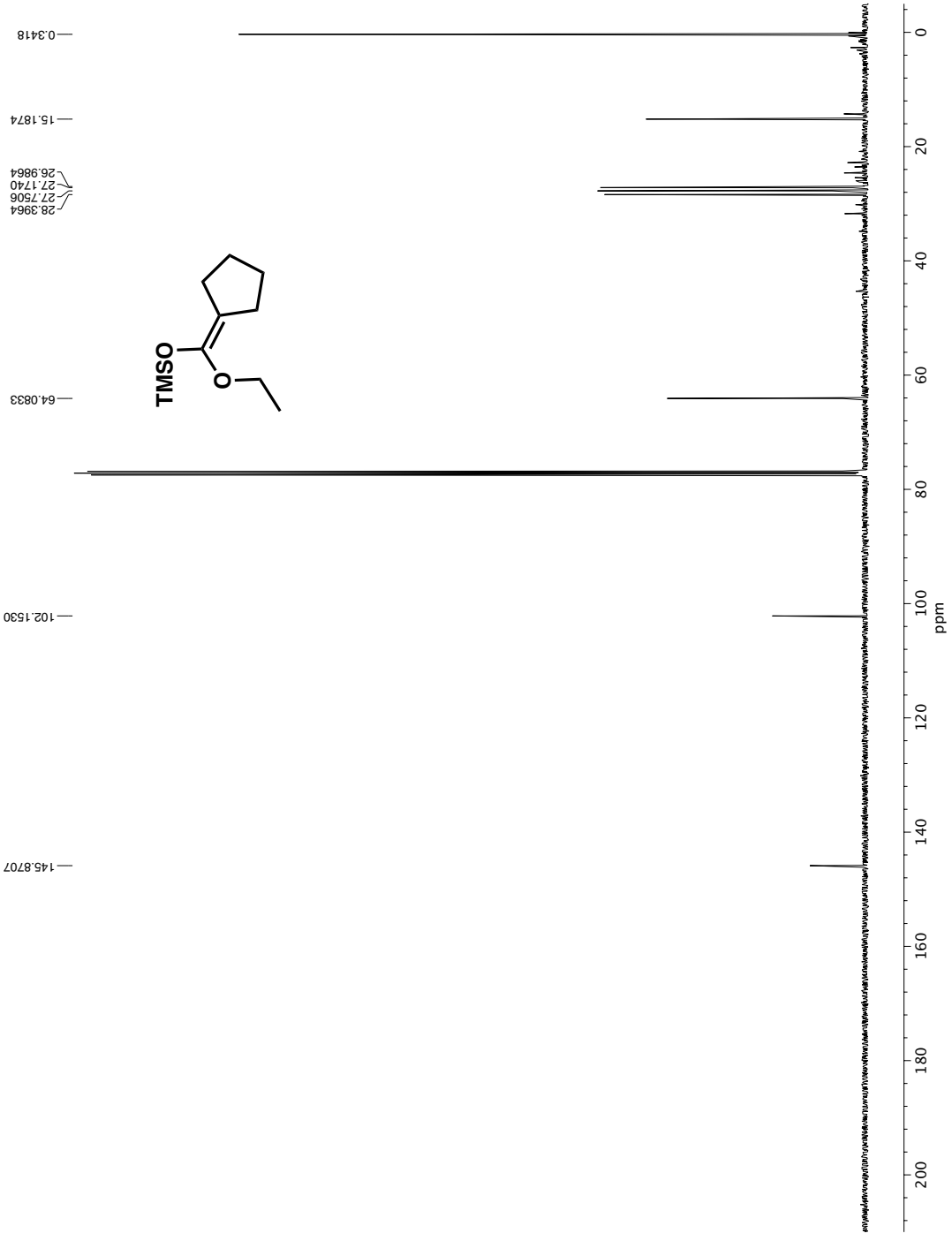
^{1}H NMR (500 MHz, $CDCl_3$) of compound **118g**.



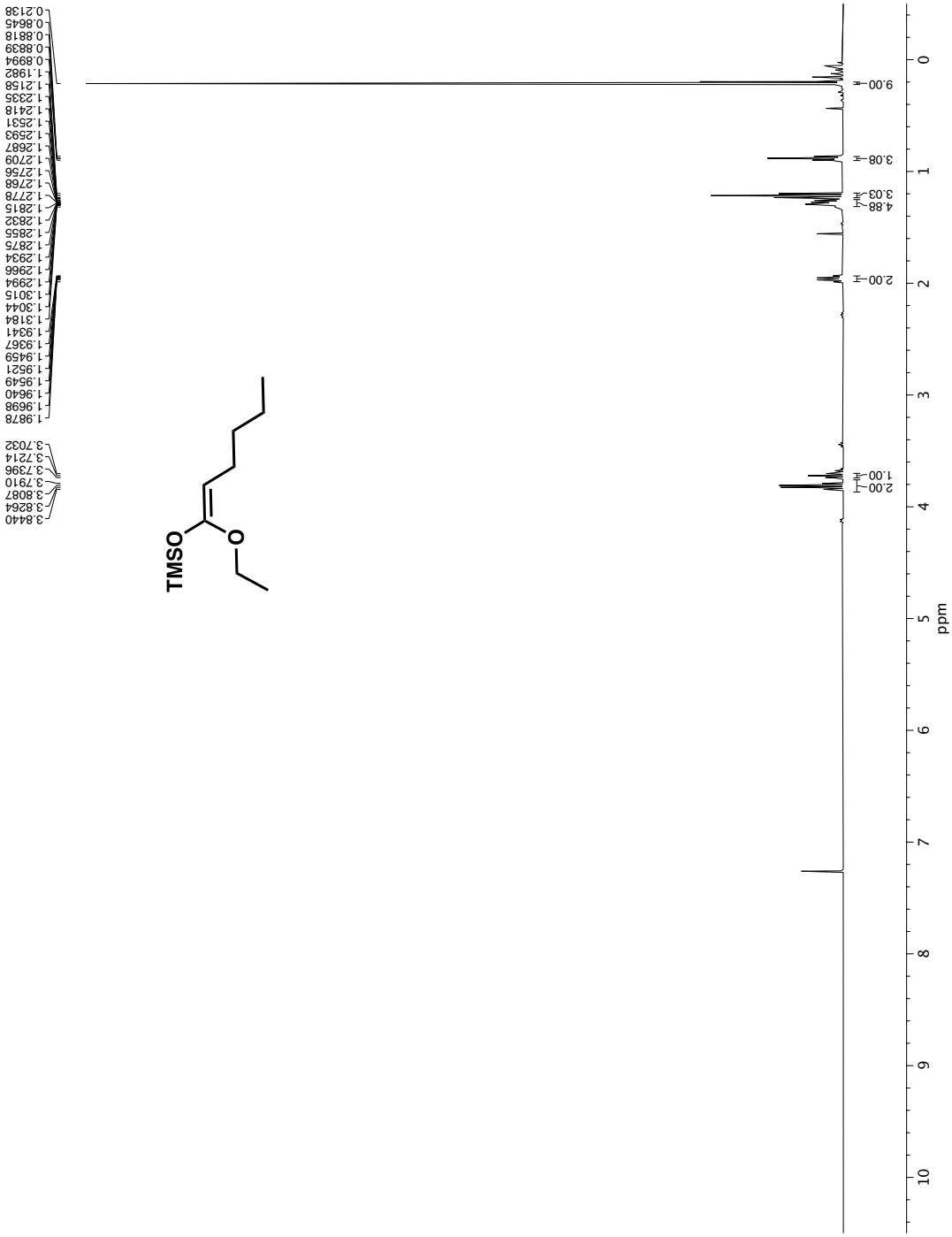
^{13}C NMR (126 MHz, $CDCl_3$) of compound **118g**.



^{1}H NMR (400 MHz, $CDCl_3$) of compound **120c**.



^{13}C NMR (101 MHz, $CDCl_3$) of compound **120c**.



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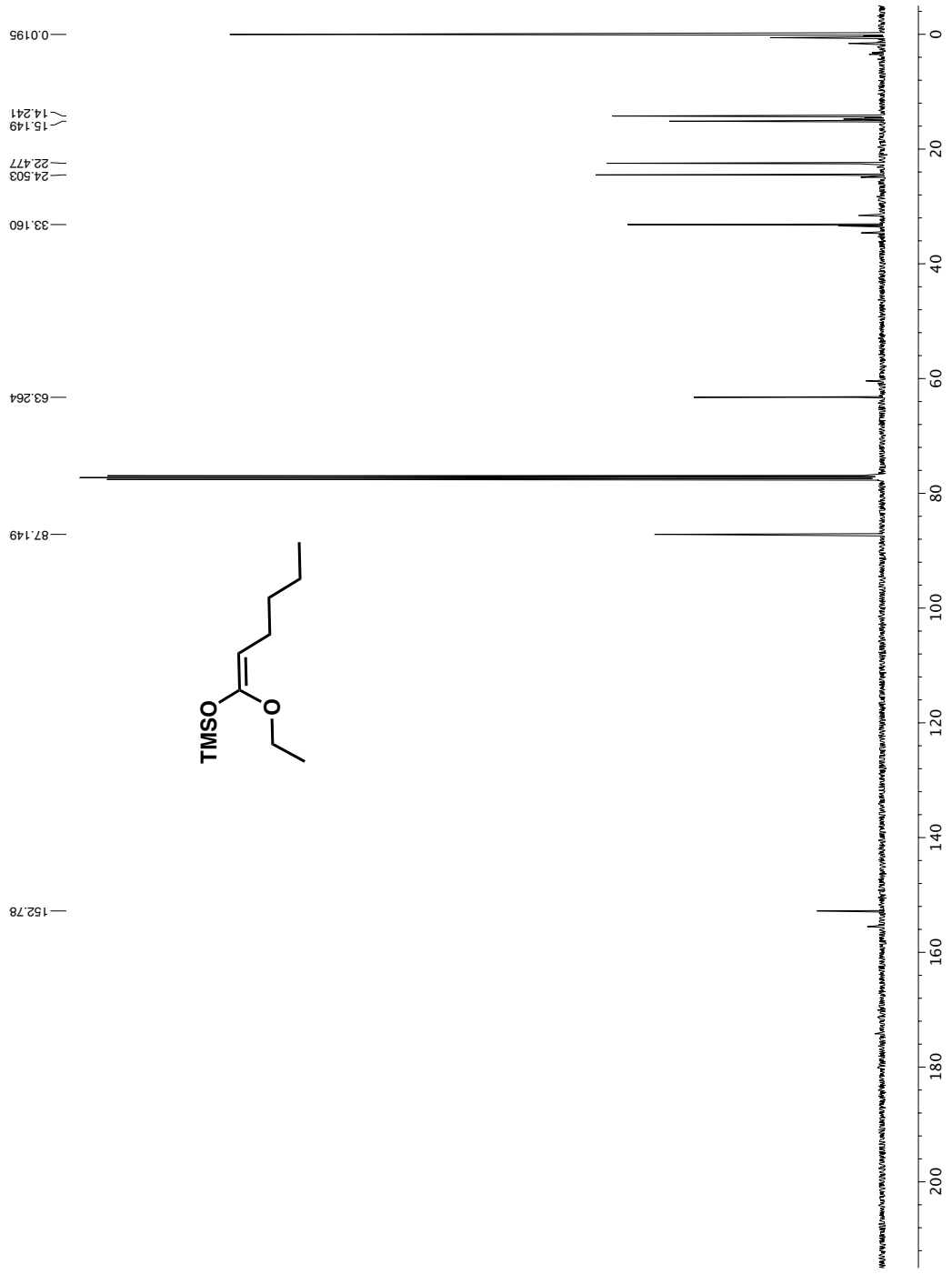
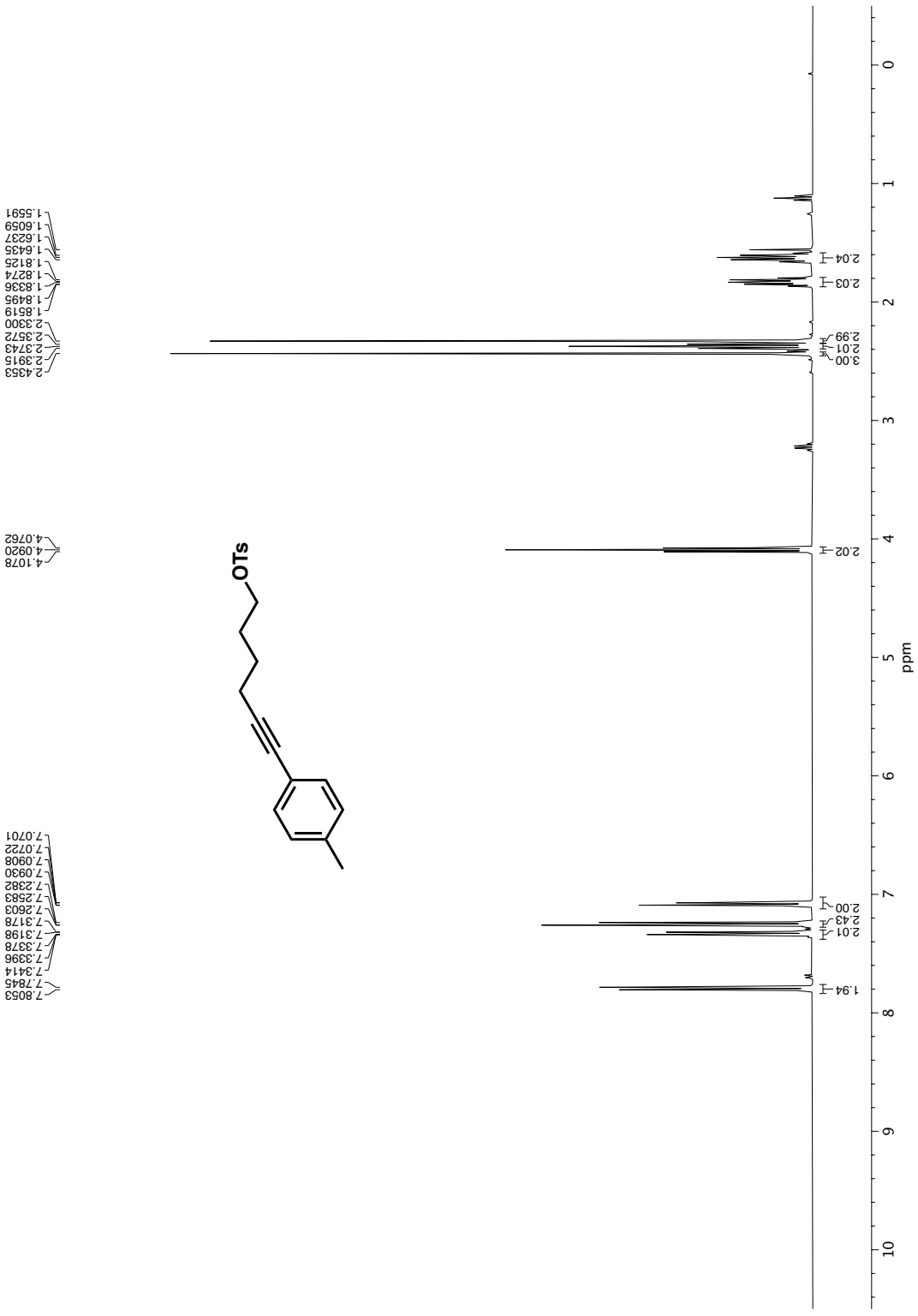


^{13}C NMR (101 MHz, $CDCl_3$) of compound **120d**.



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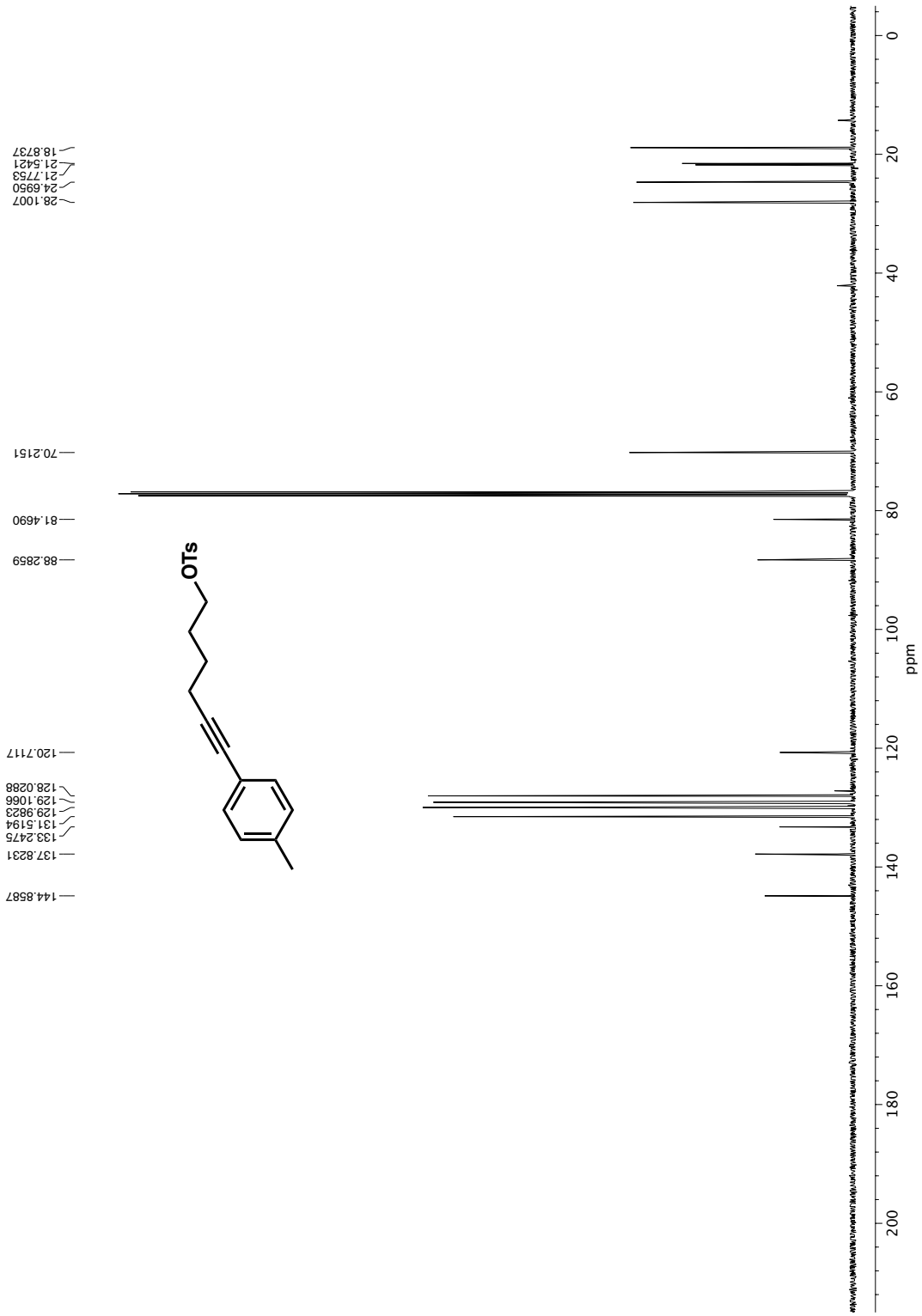

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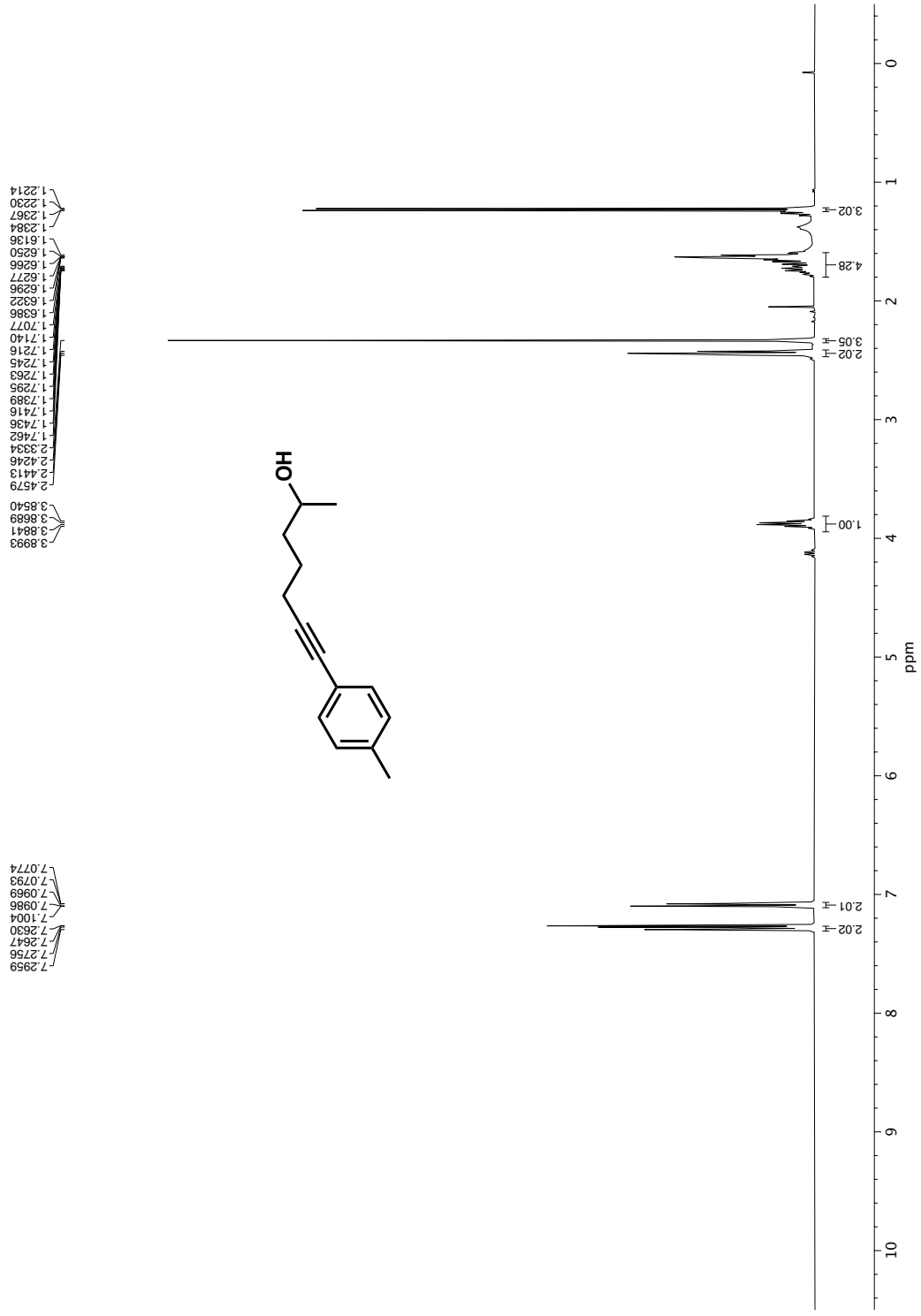
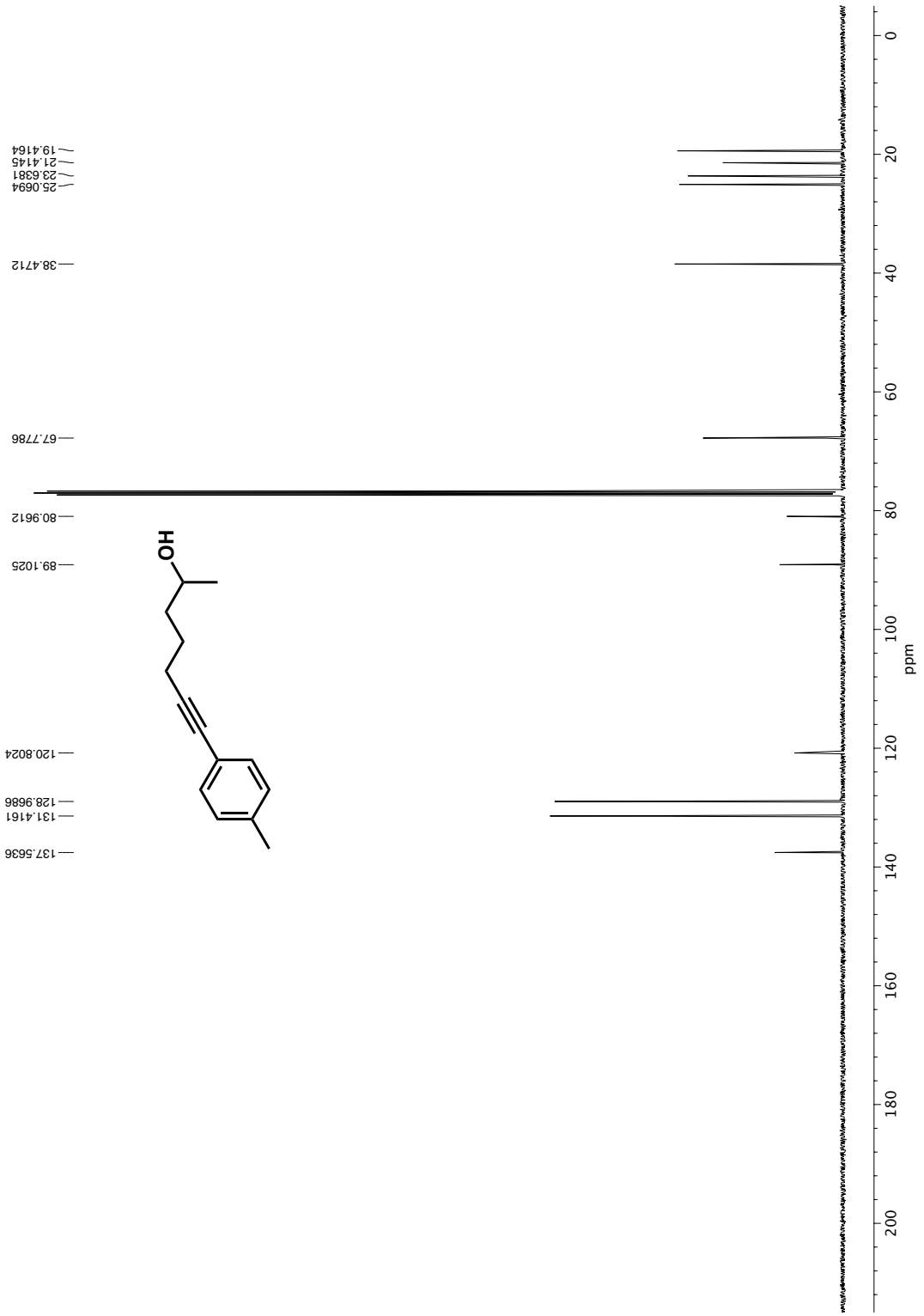
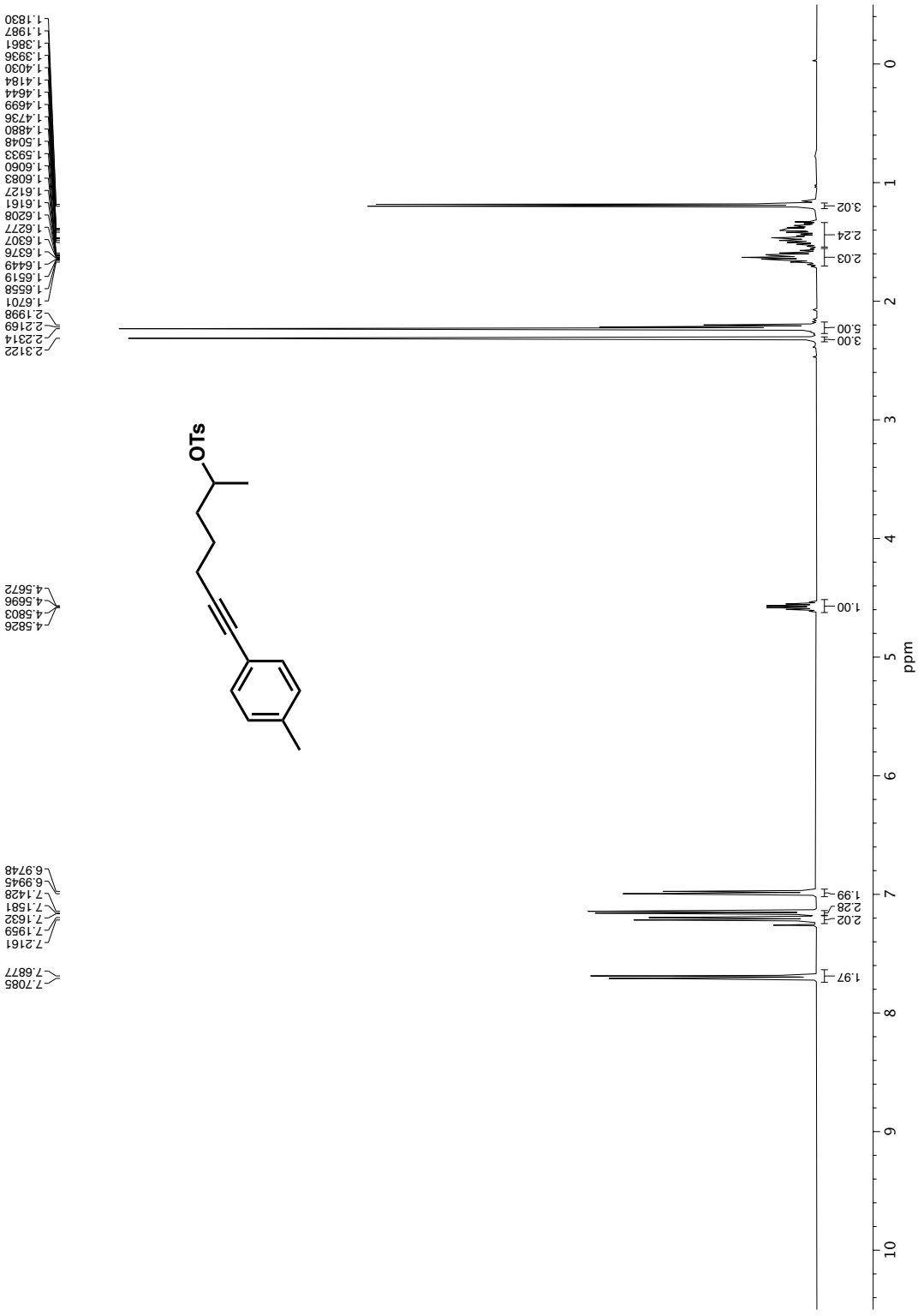


^{1}H NMR (400 MHz, $CDCl_3$) of compound **141**.



^{13}C NMR (101 MHz, $CDCl_3$) of compound **141**.



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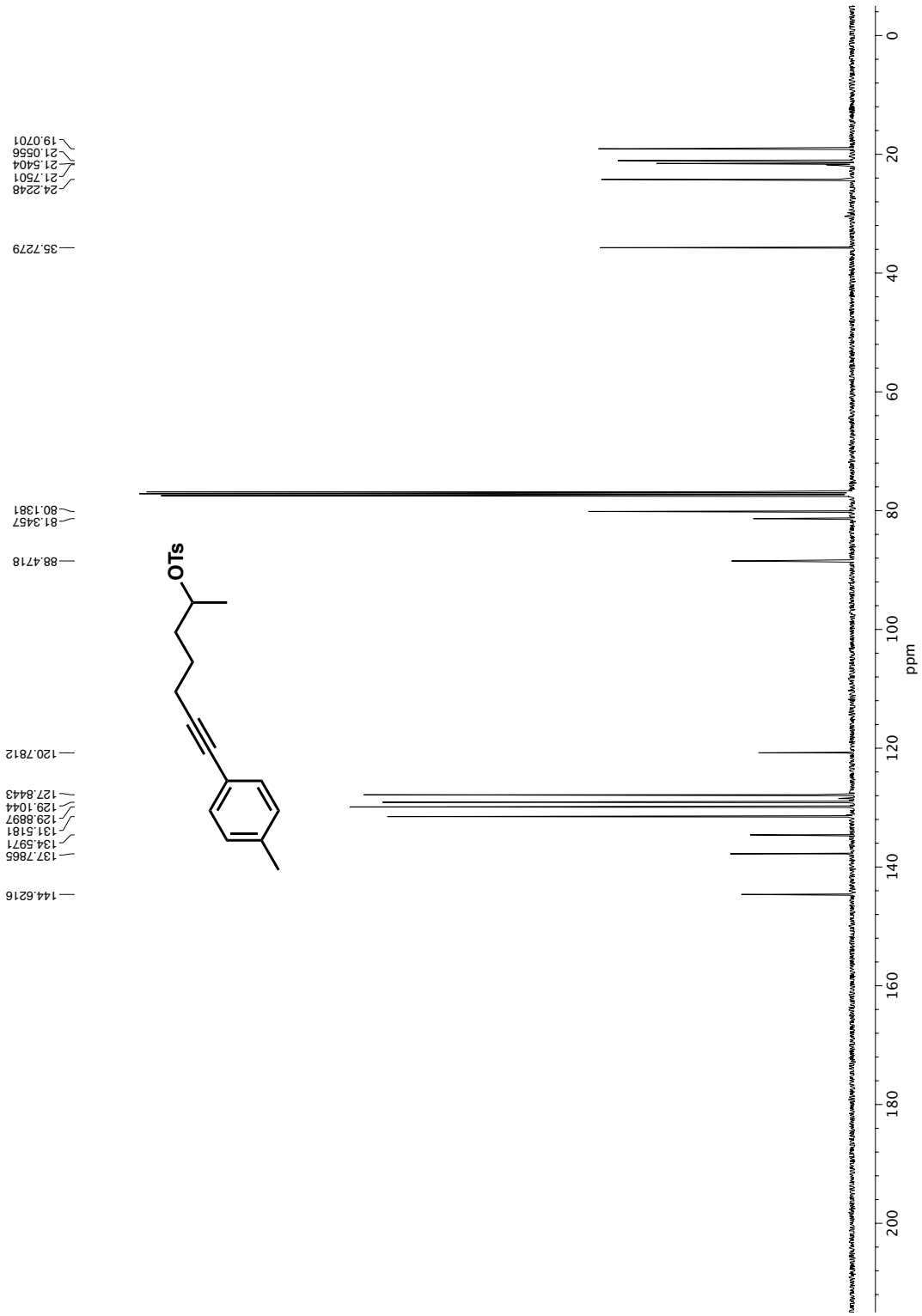
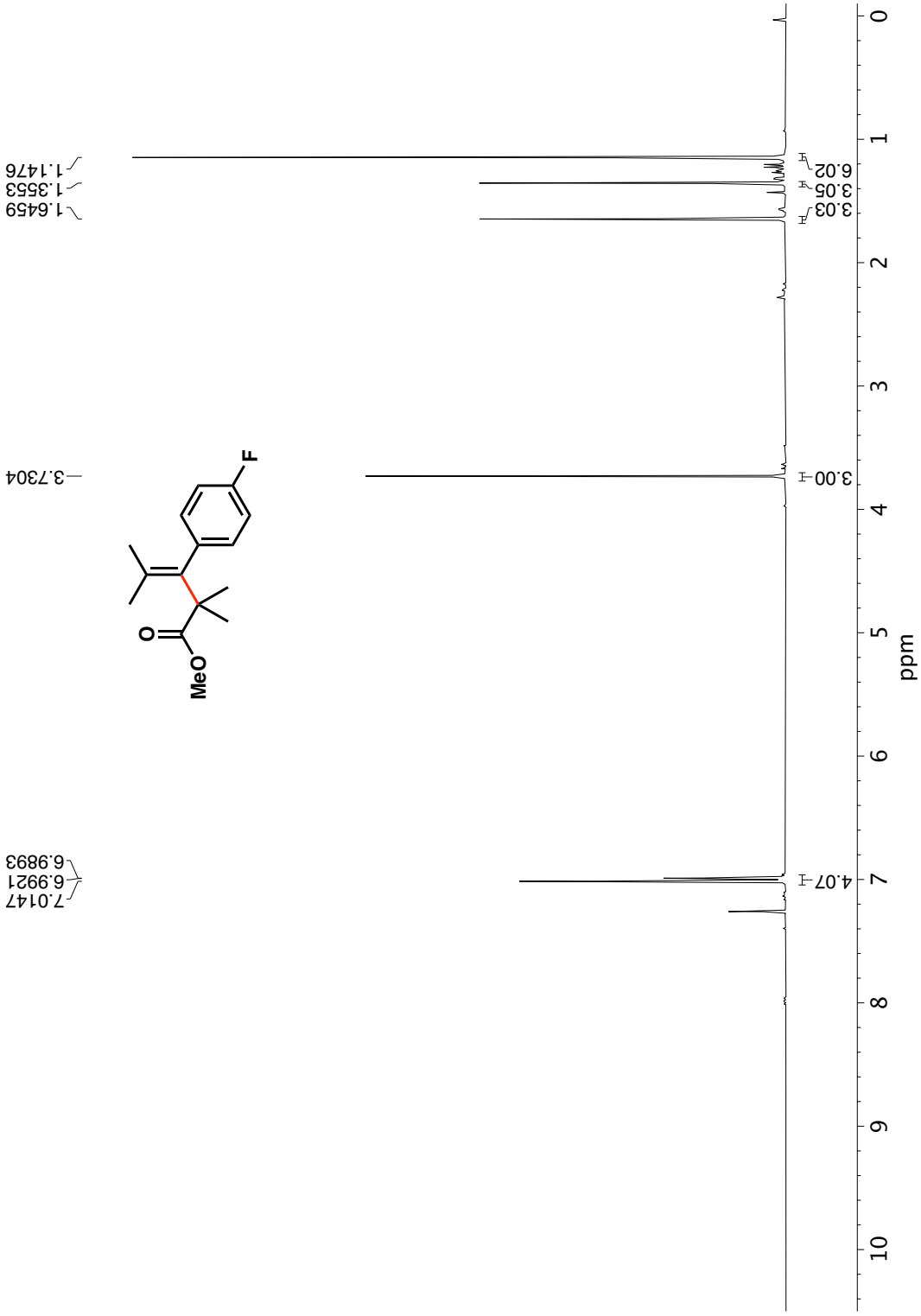
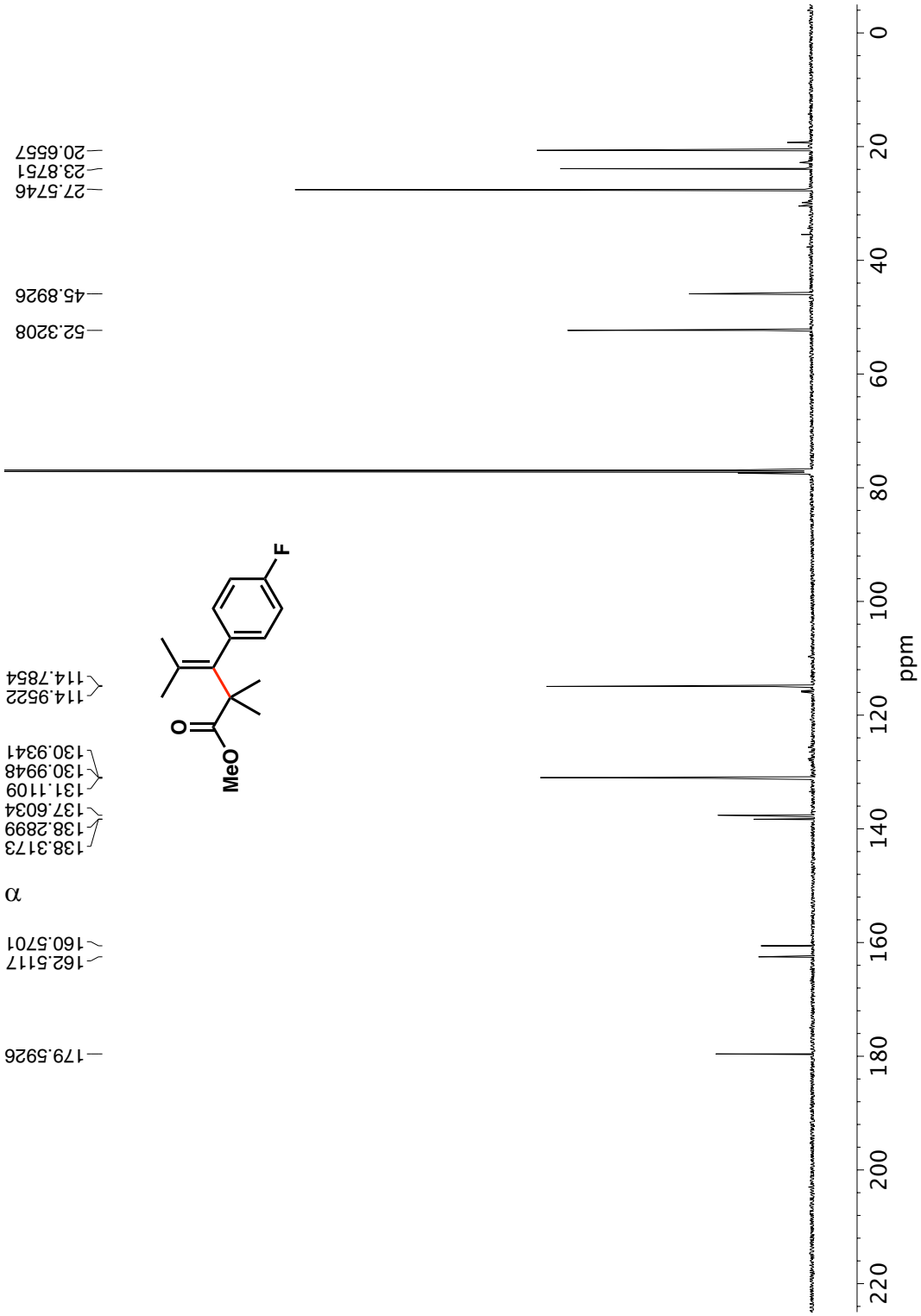


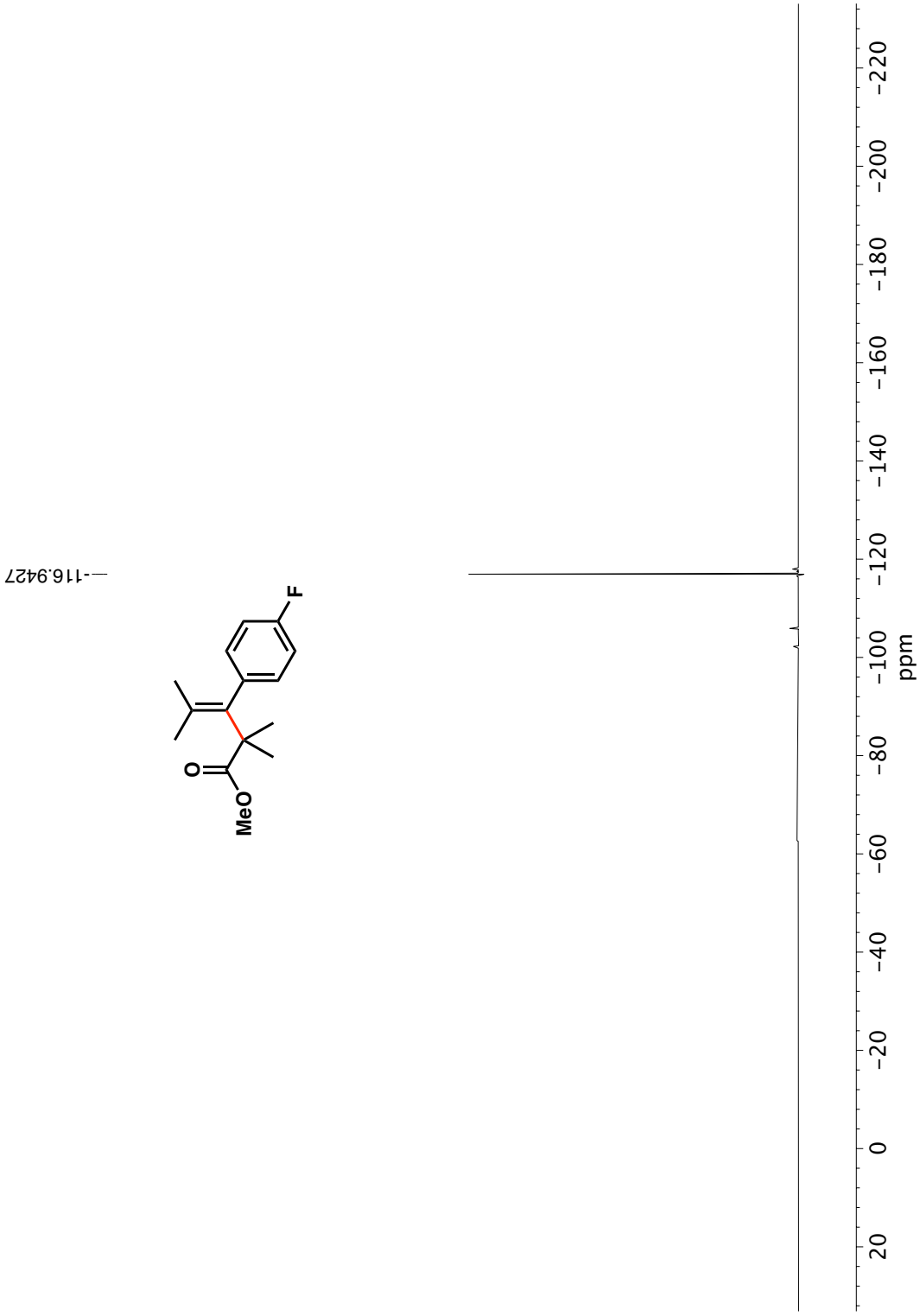
^{13}C NMR (101 MHz, $CDCl_3$) of compound **130b**.



^{1}H NMR (300 MHz, $CDCl_3$) of compound **117a.**

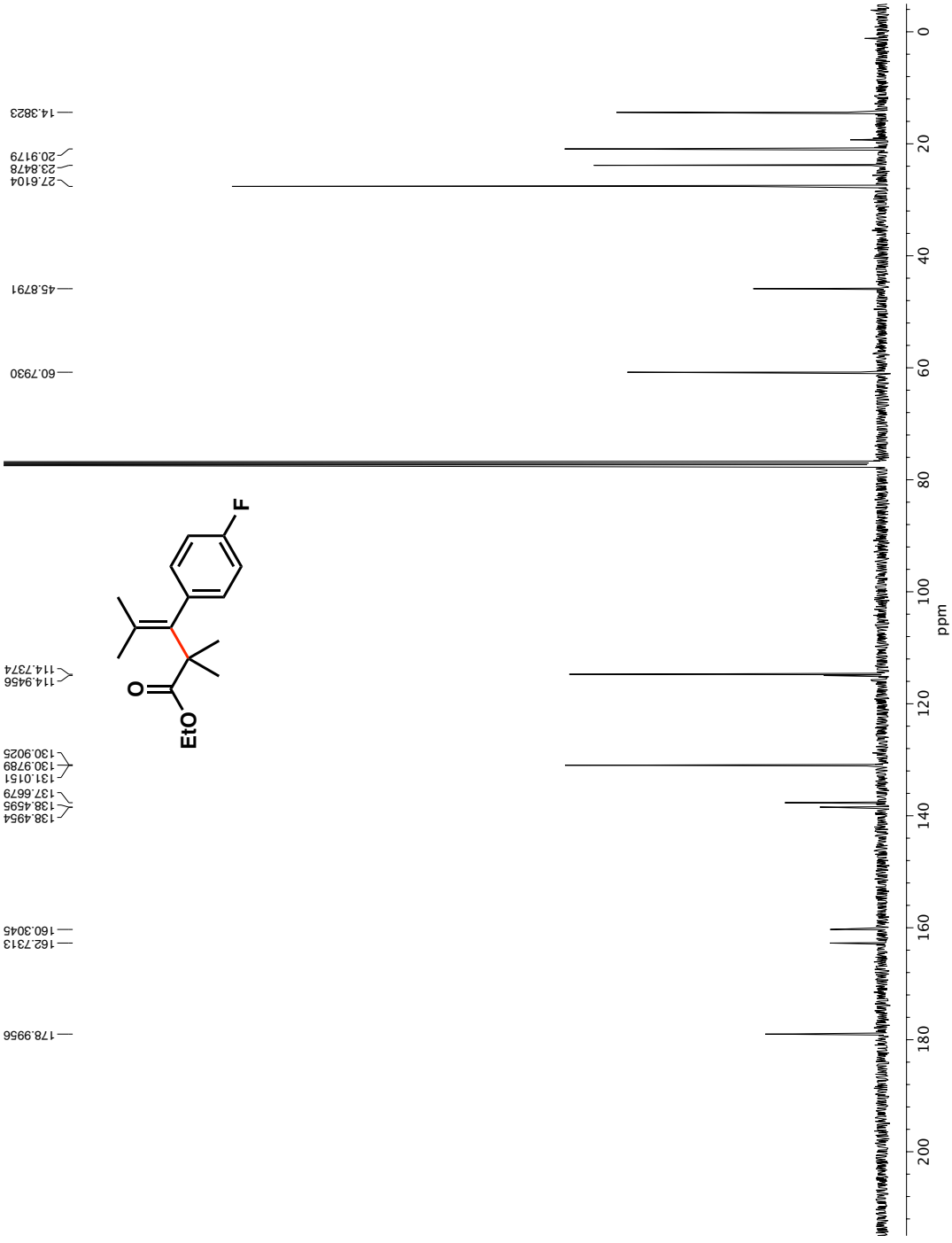


^{13}C NMR (126 MHz, $CDCl_3$) of compound **117a**.

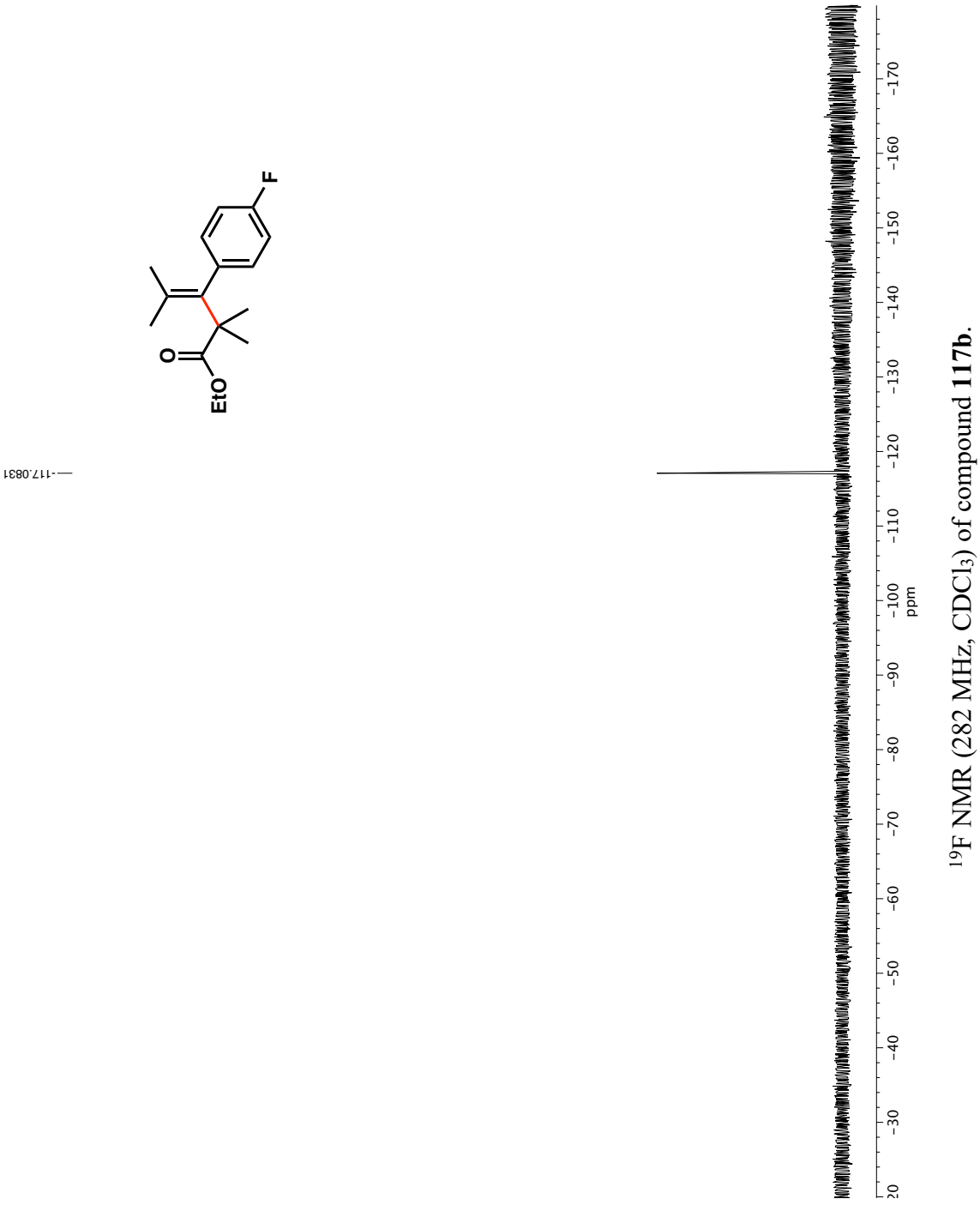


^{19}F NMR (282 MHz, $CDCl_3$) of compound **117a**.

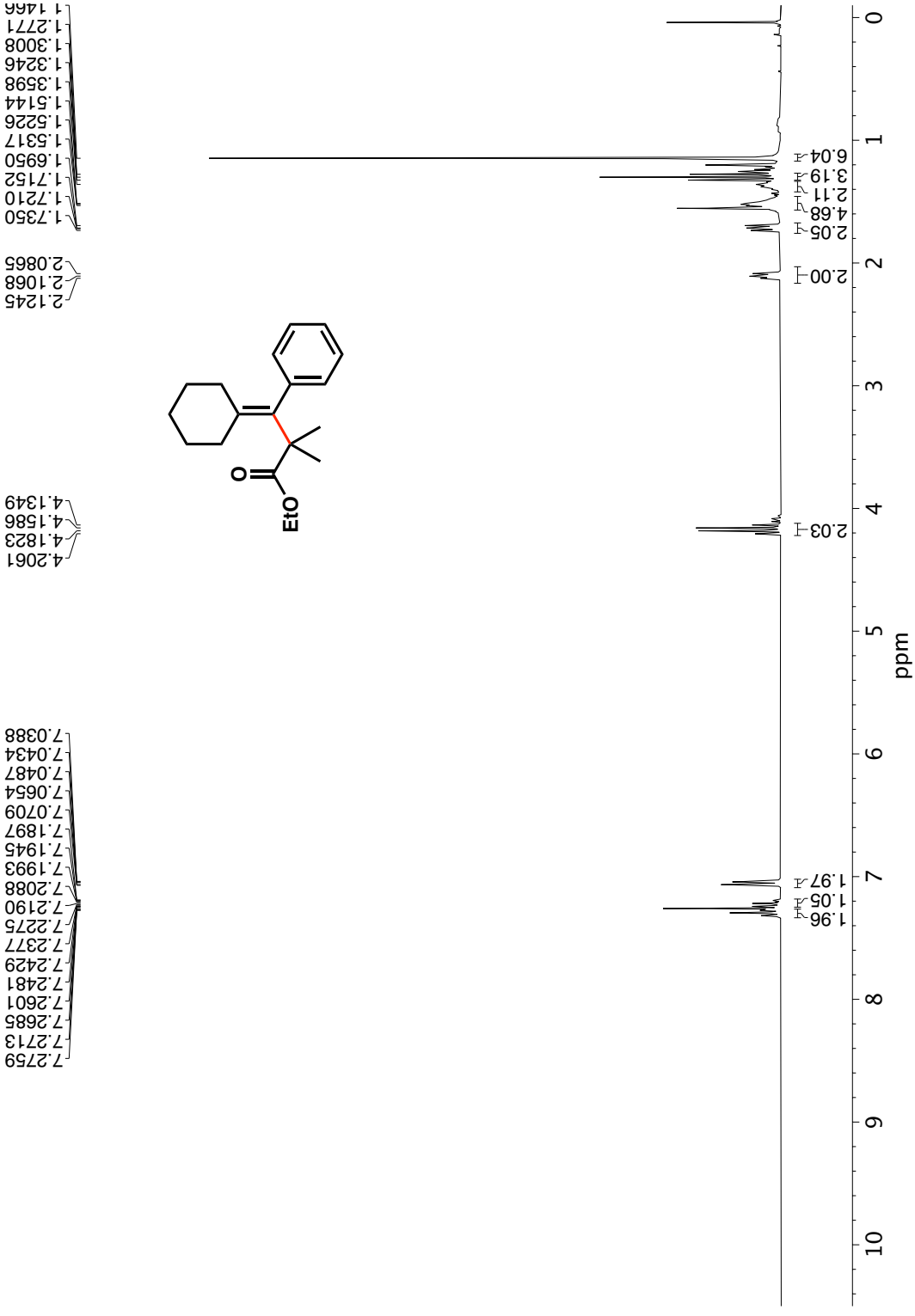
^{1}H NMR (400 MHz, $CDCl_3$) of compound **117b.**



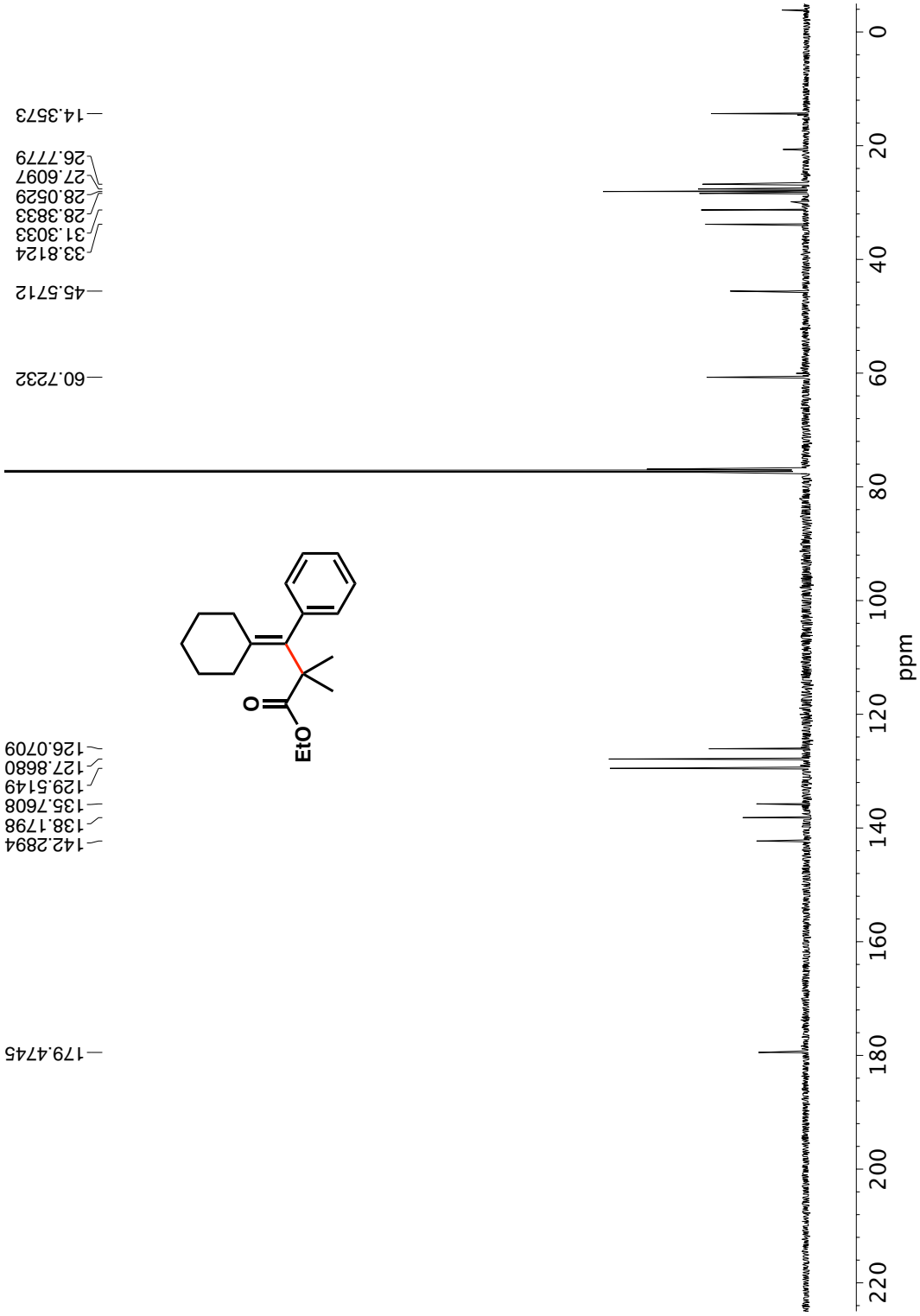
^{13}C NMR (101 MHz, $CDCl_3$) of compound **117b**.



^{19}F NMR (282 MHz, $CDCl_3$) of compound **117b**.



^{1}H NMR (300 MHz, $CDCl_3$) of compound **119a**.



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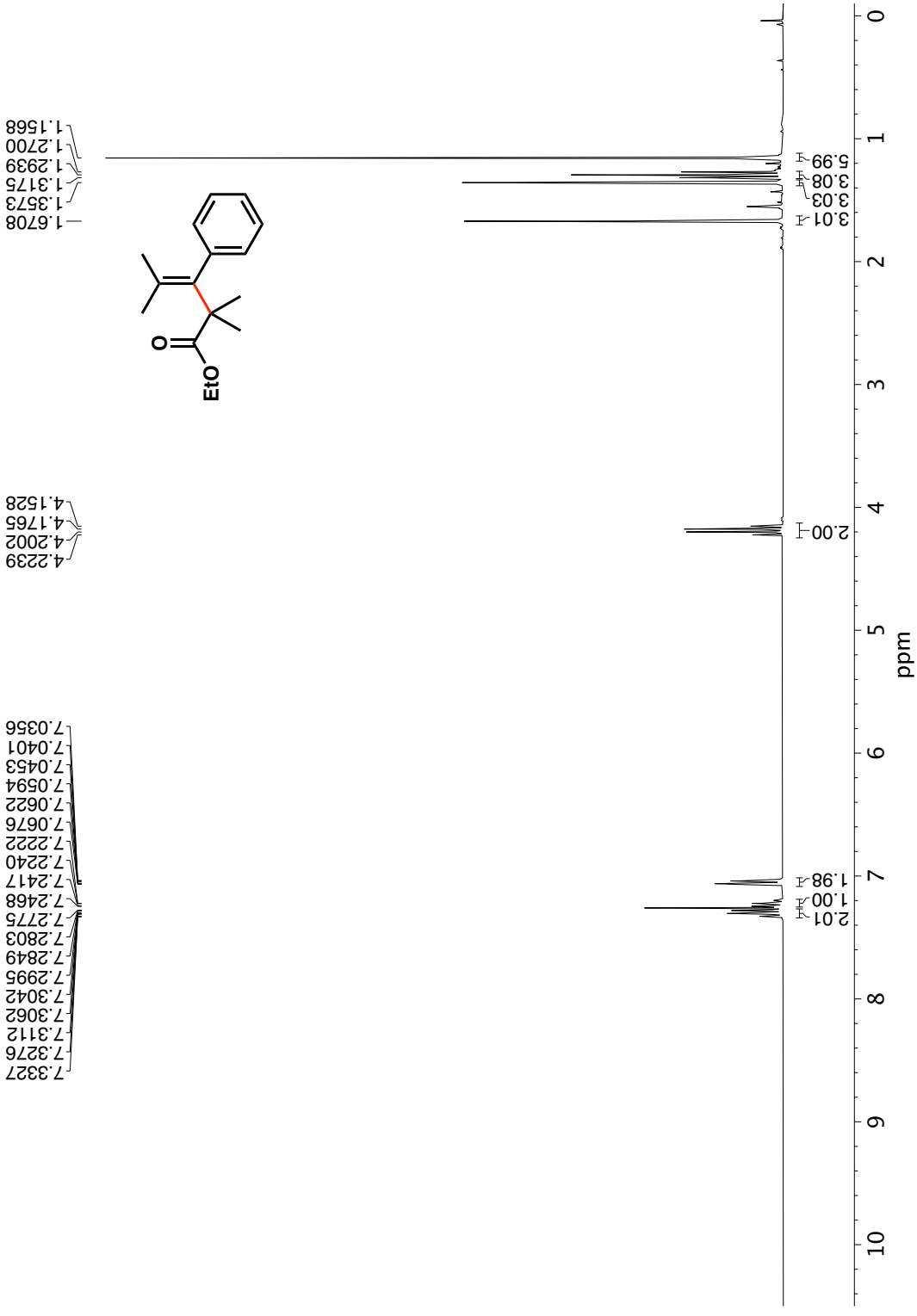
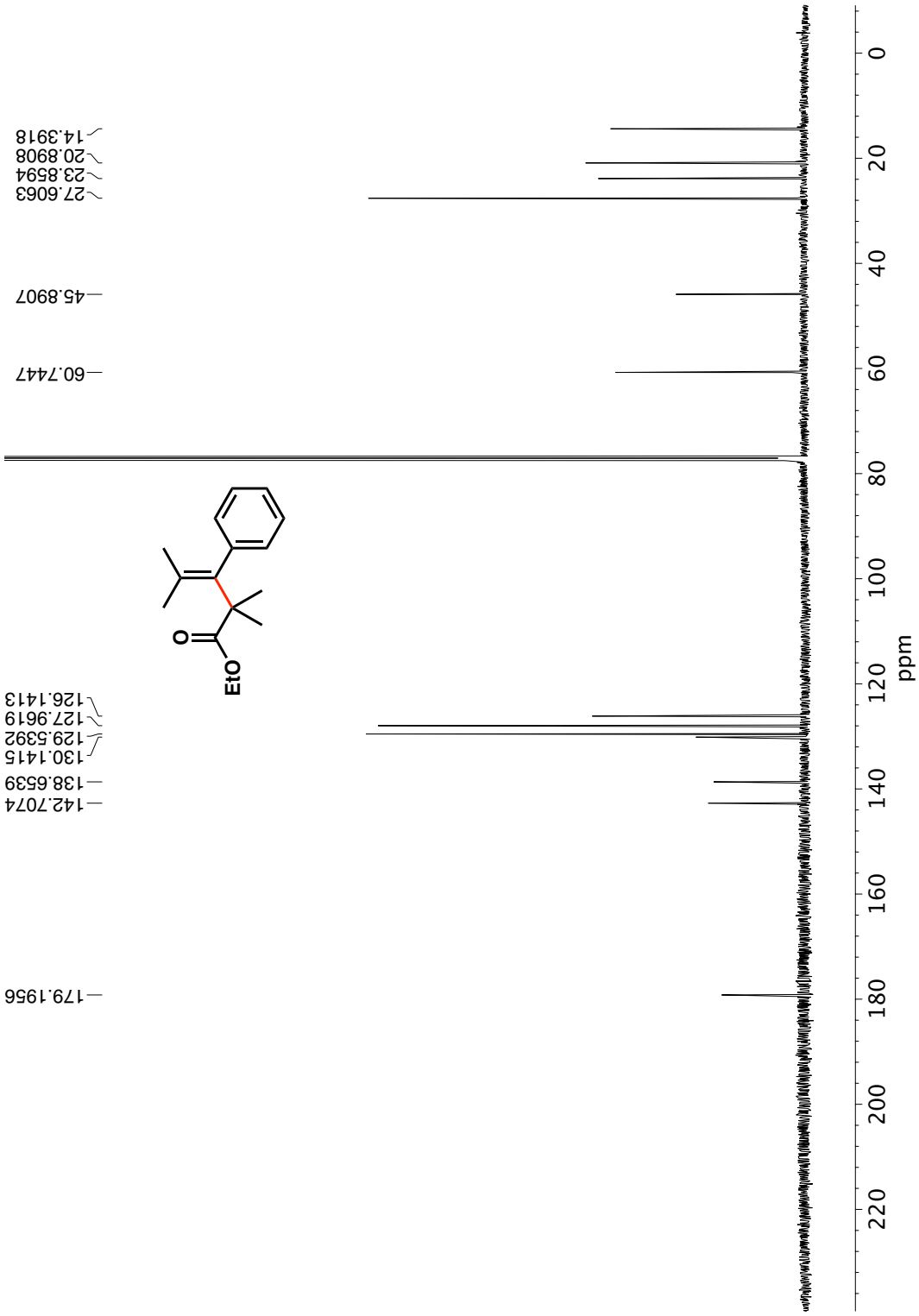
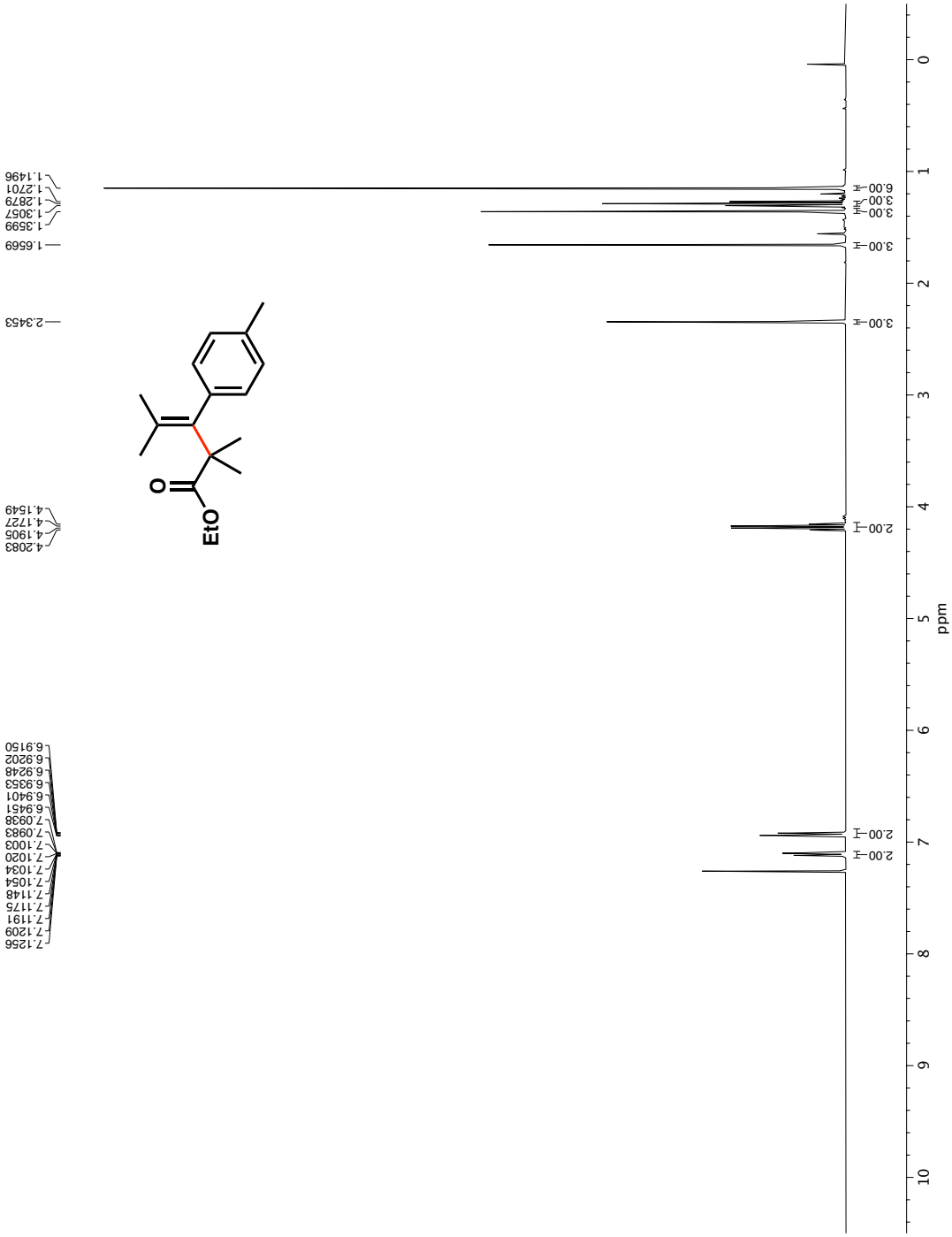


^{1}H NMR (300 MHz, $CDCl_3$) of compound **119b**.



^{13}C NMR (500 MHz, $CDCl_3$) of compound **119b**.



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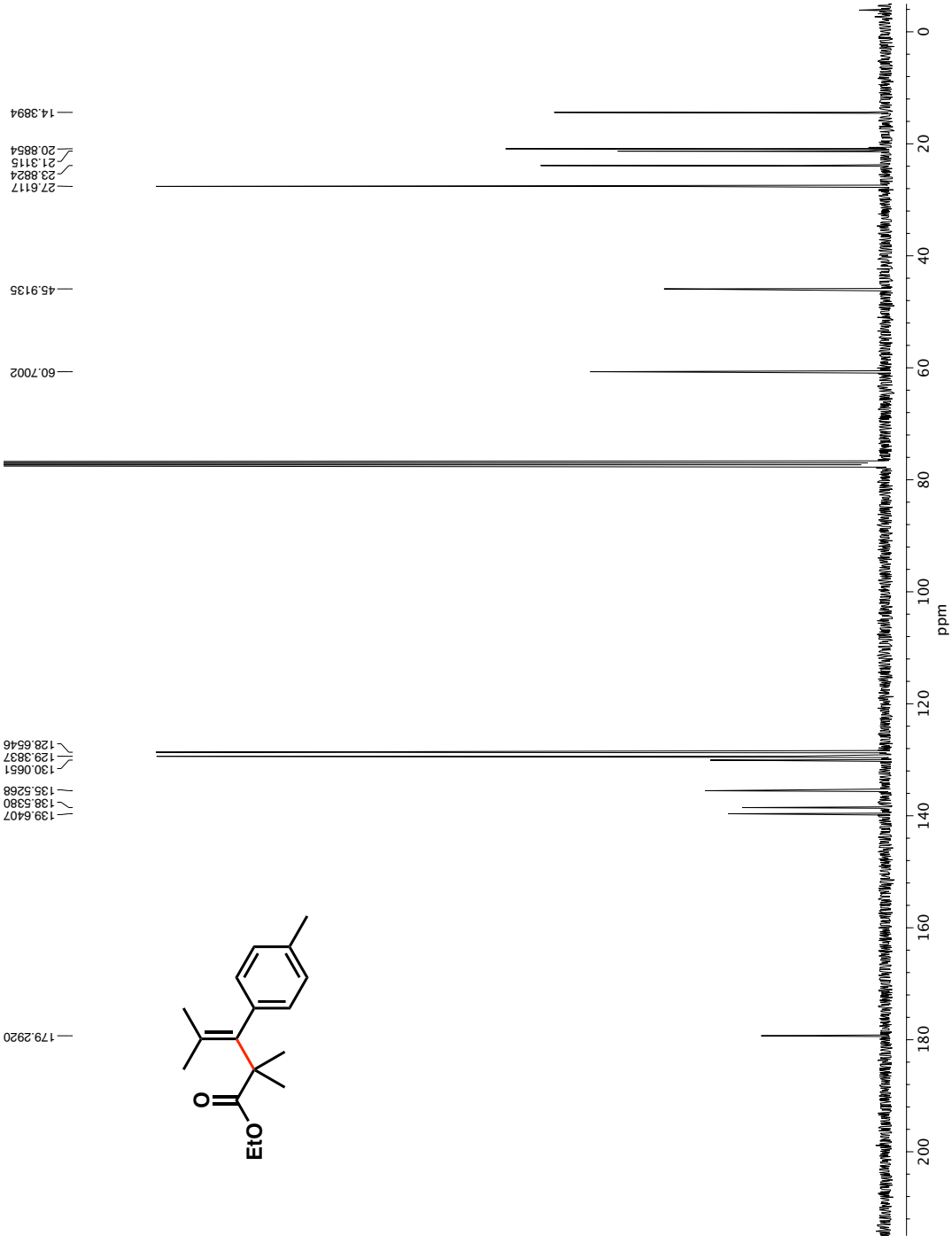
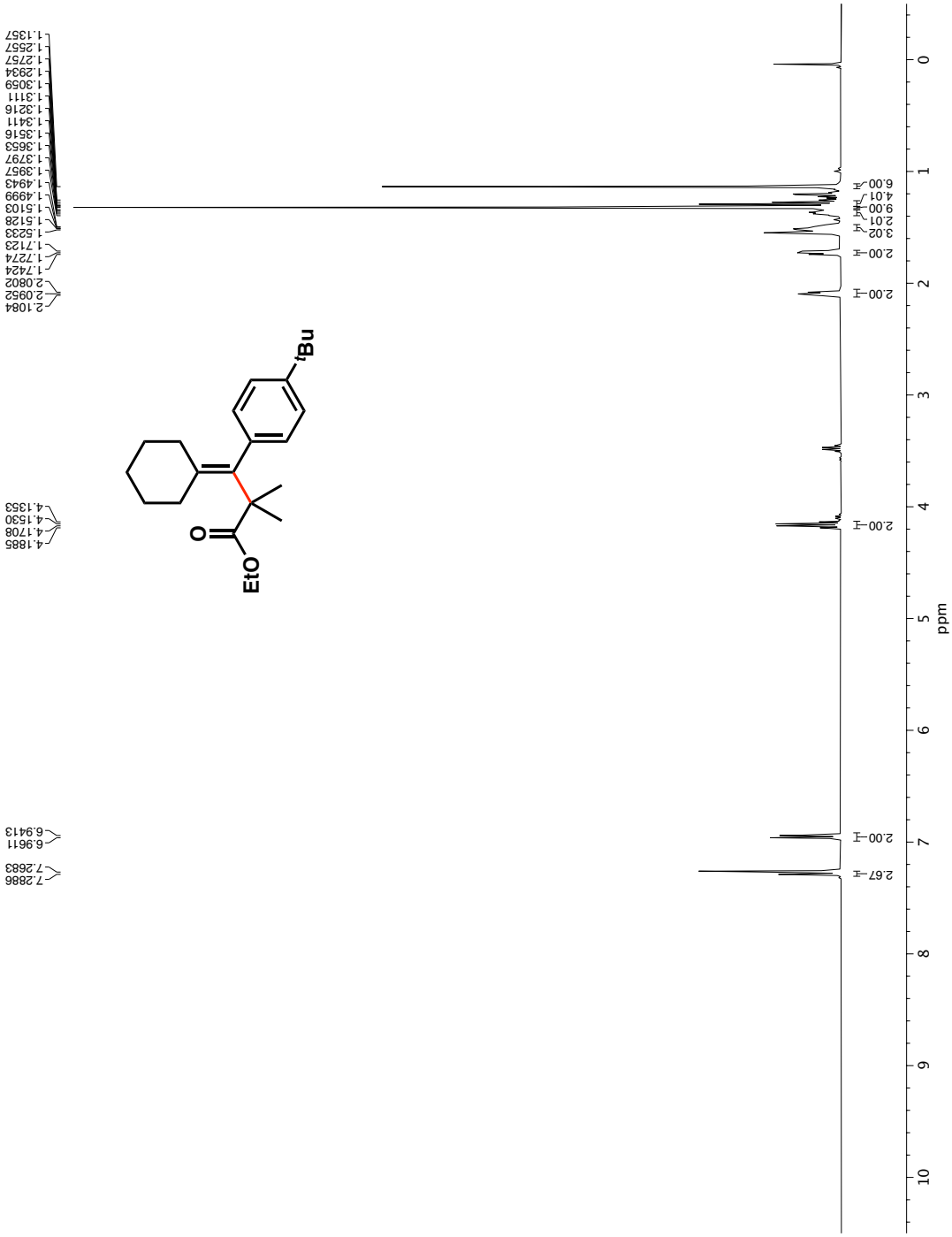
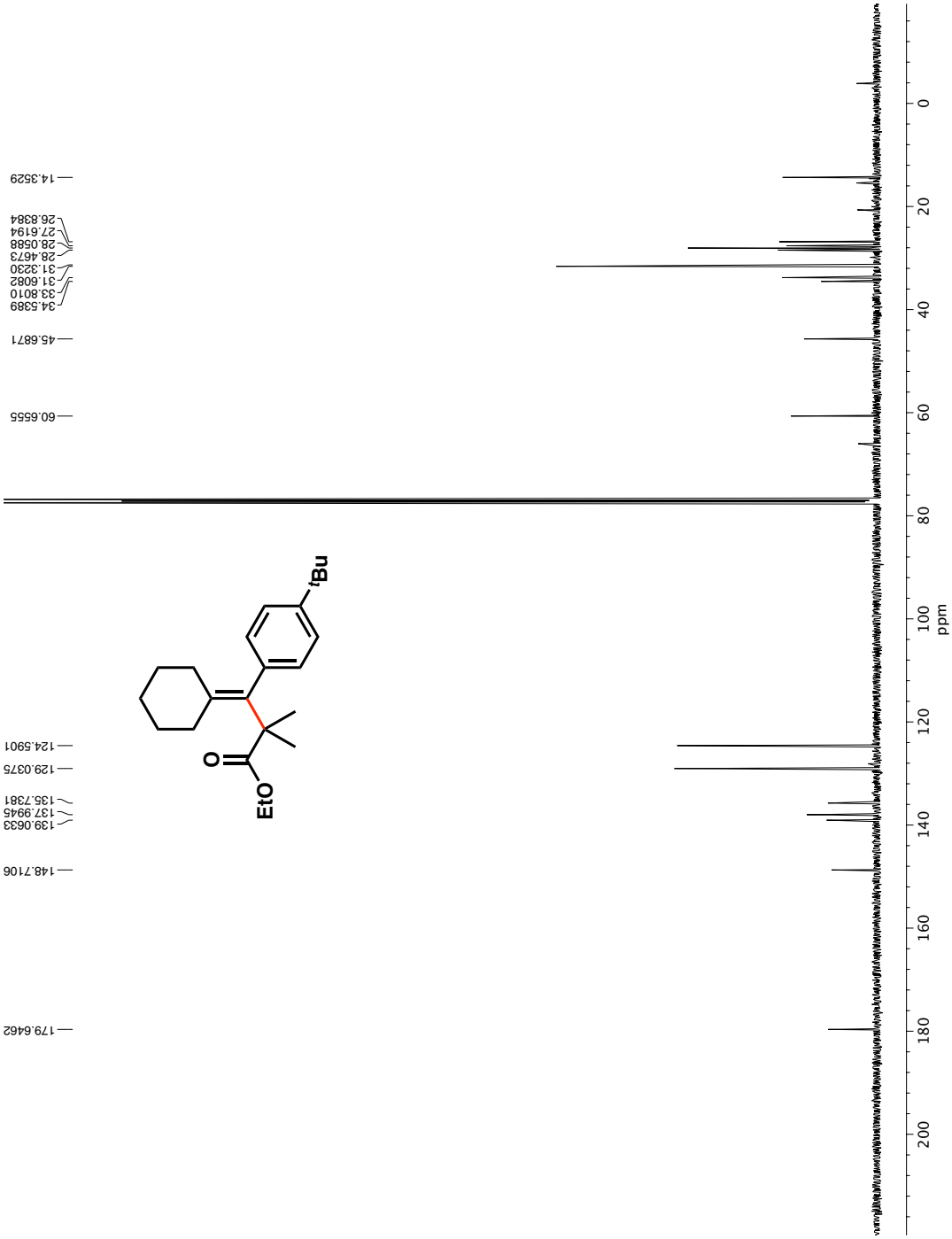


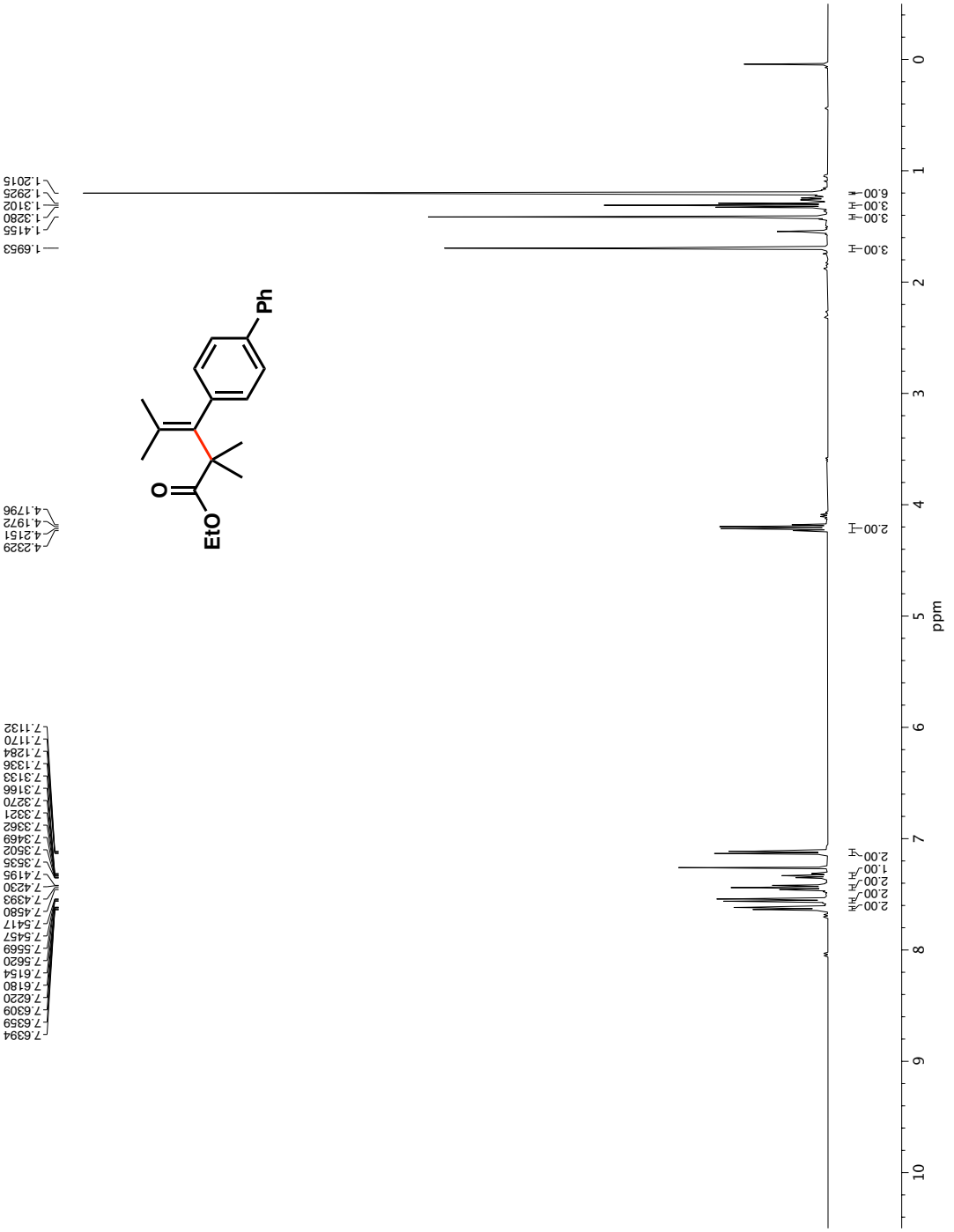
^{13}C NMR (400 MHz, $CDCl_3$) of compound **119c**.



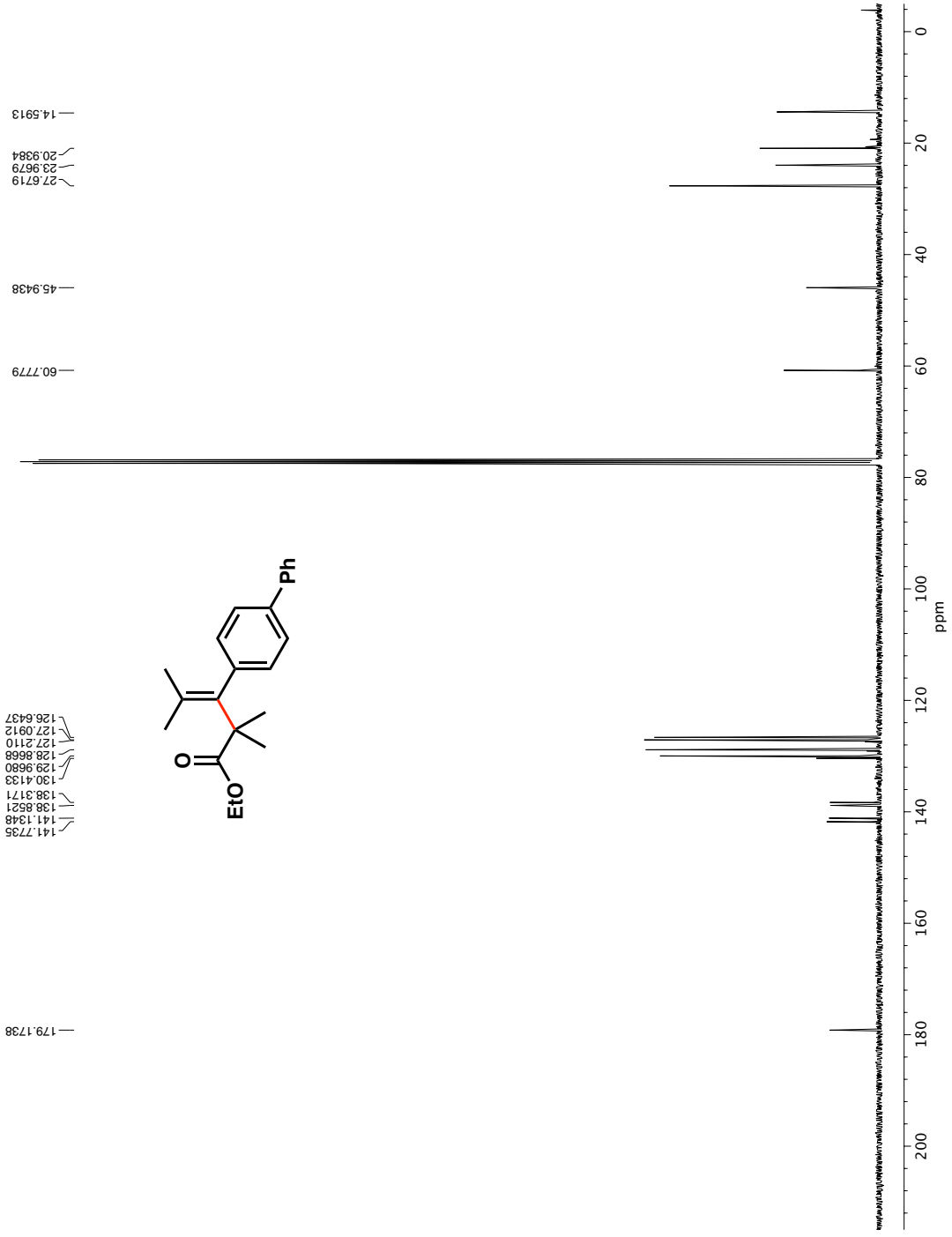
^{1}H NMR (400 MHz, $CDCl_3$) of compound **119d**.



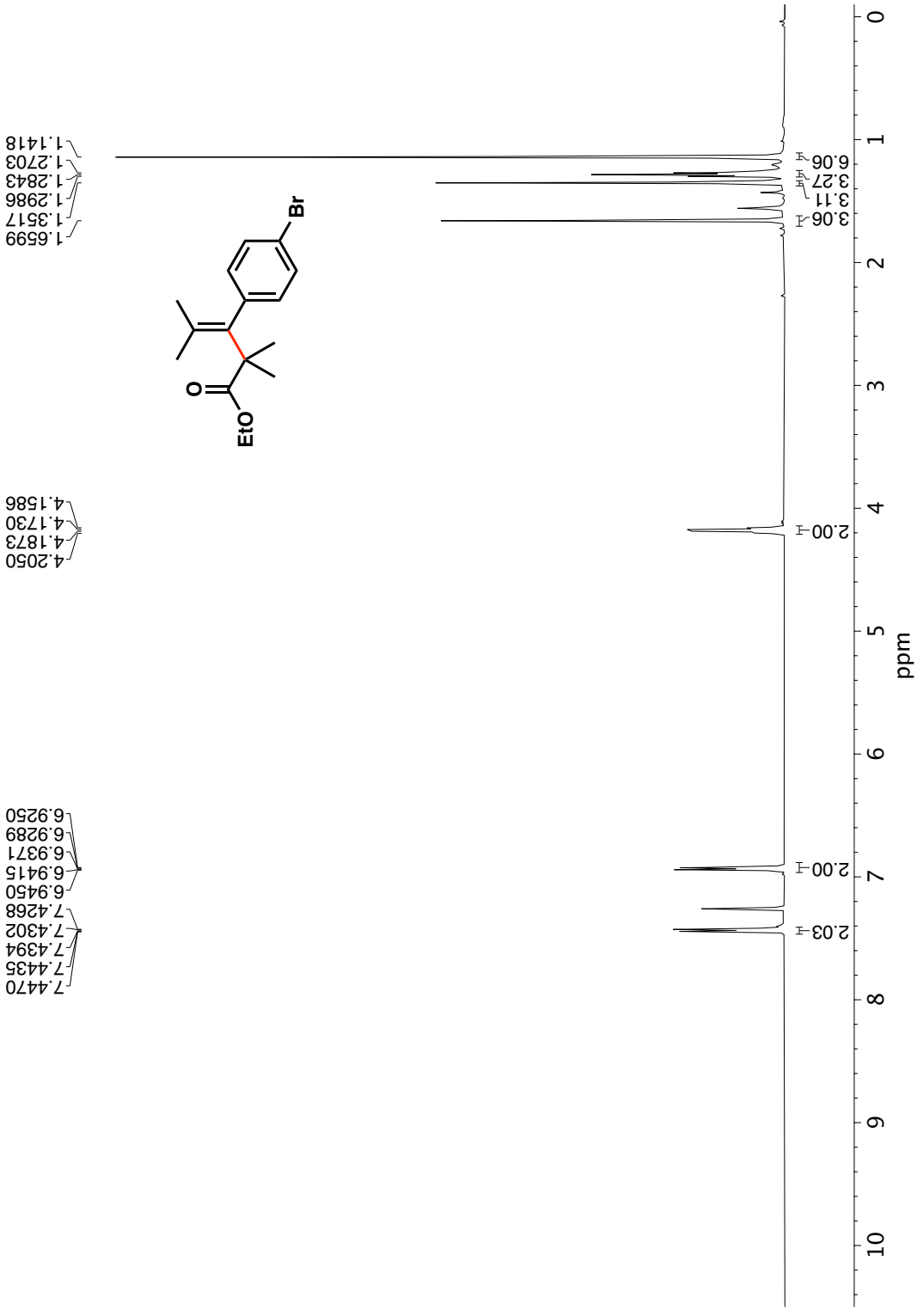
^{13}C NMR (400 MHz, $CDCl_3$) of compound **119d**.



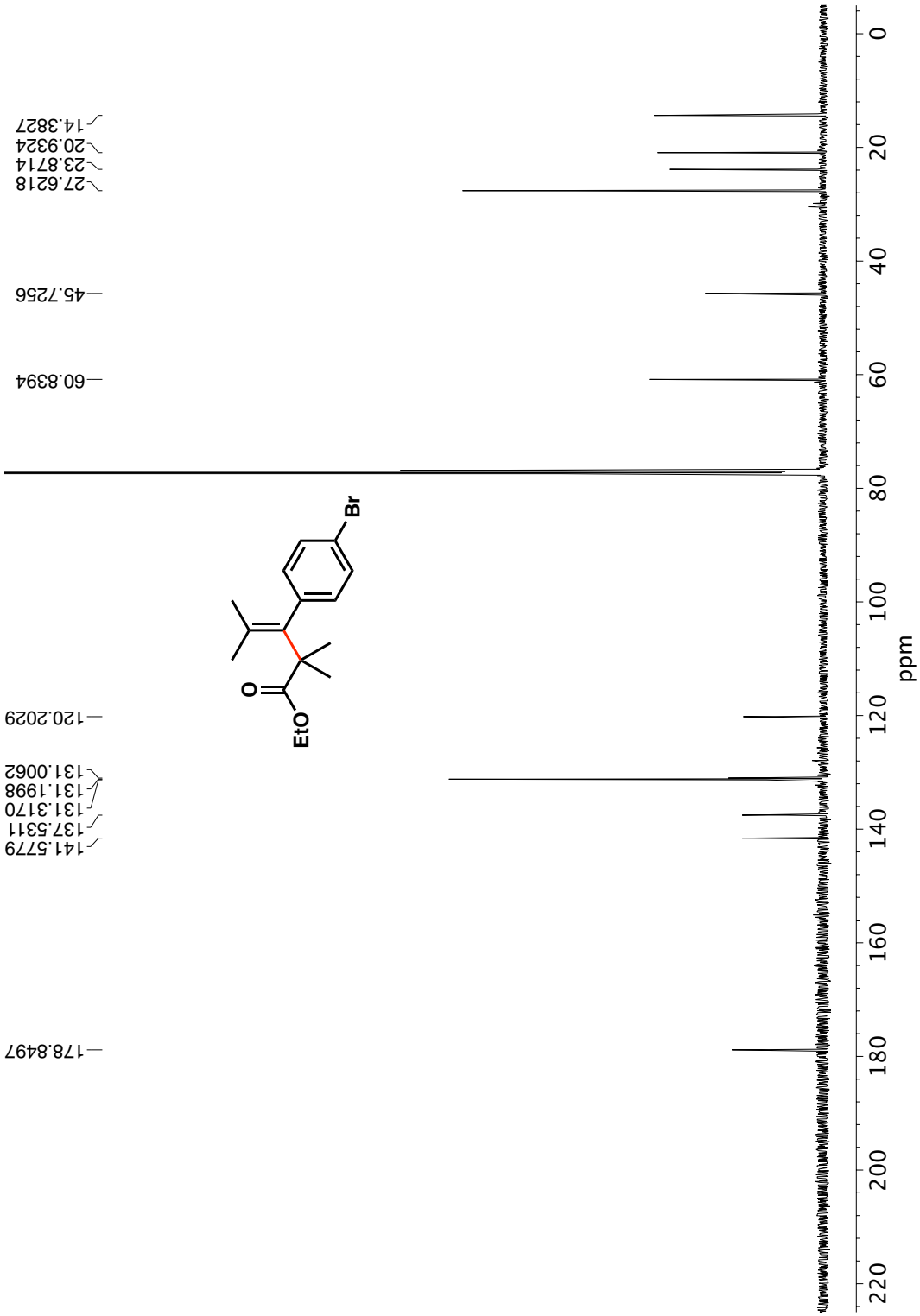
^{1}H NMR (400 MHz, $CDCl_3$) of compound **119e**.



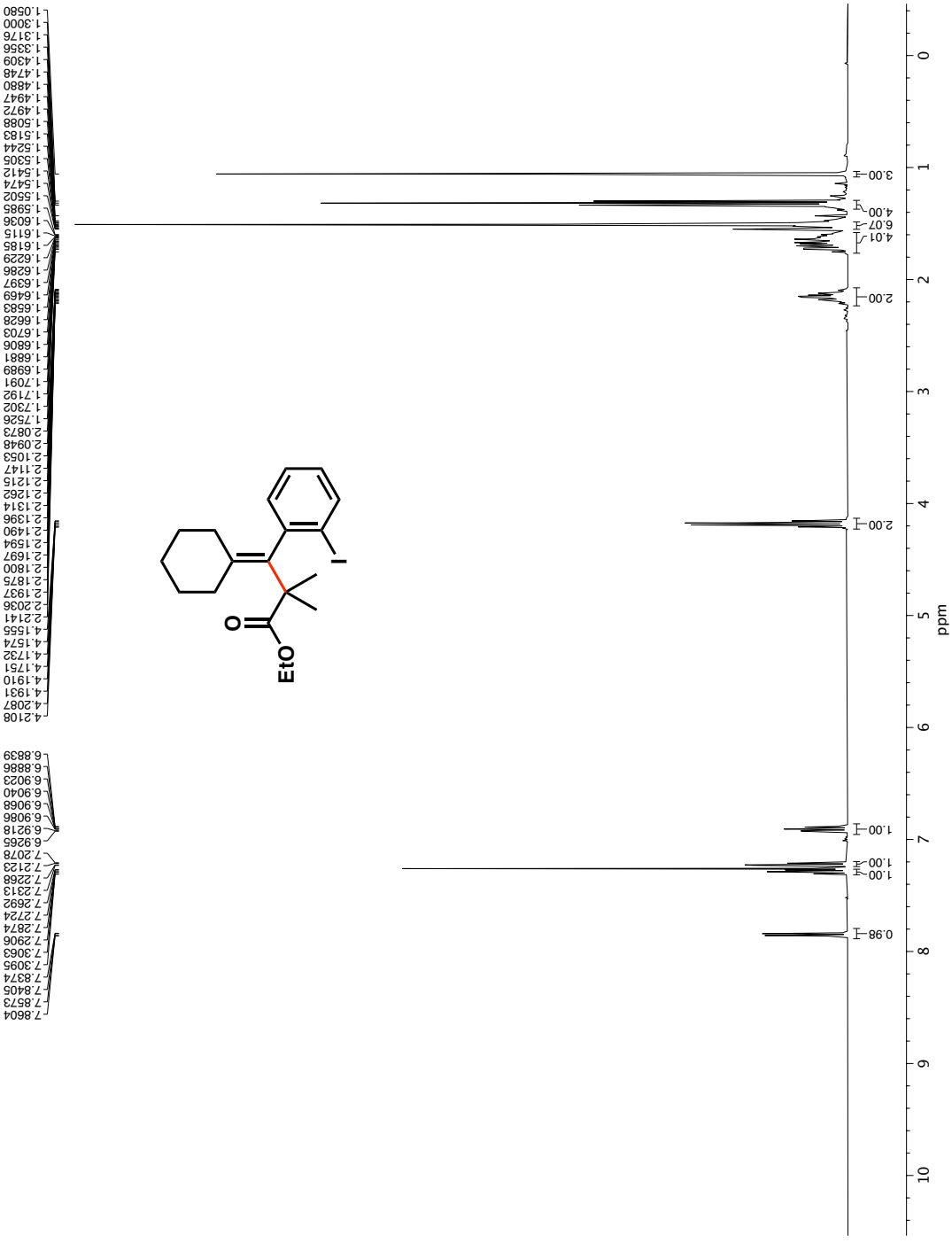
^{13}C NMR (400 MHz, $CDCl_3$) of compound **119e**.



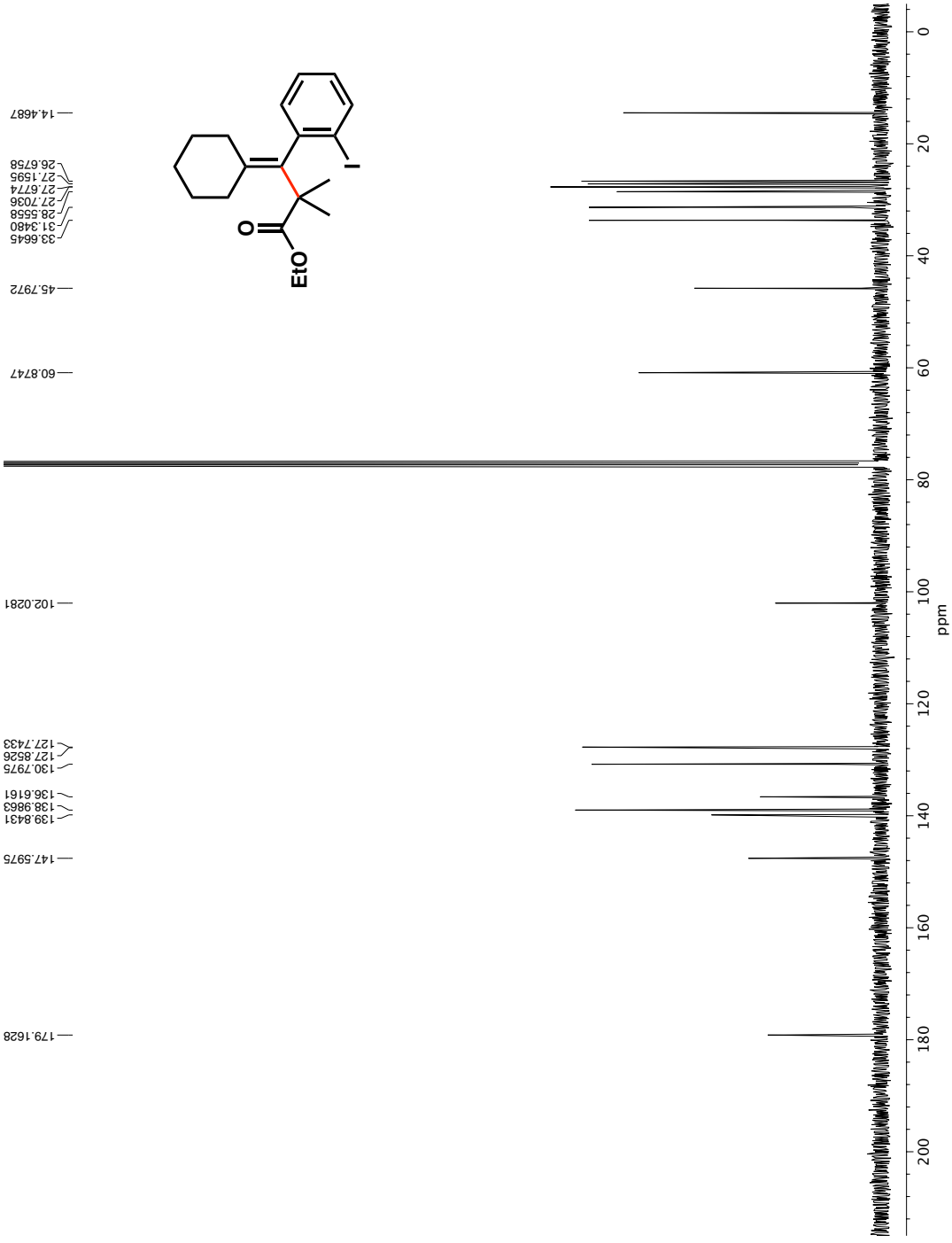
^{1}H NMR (500 MHz, $CDCl_3$) of compound **119f**.



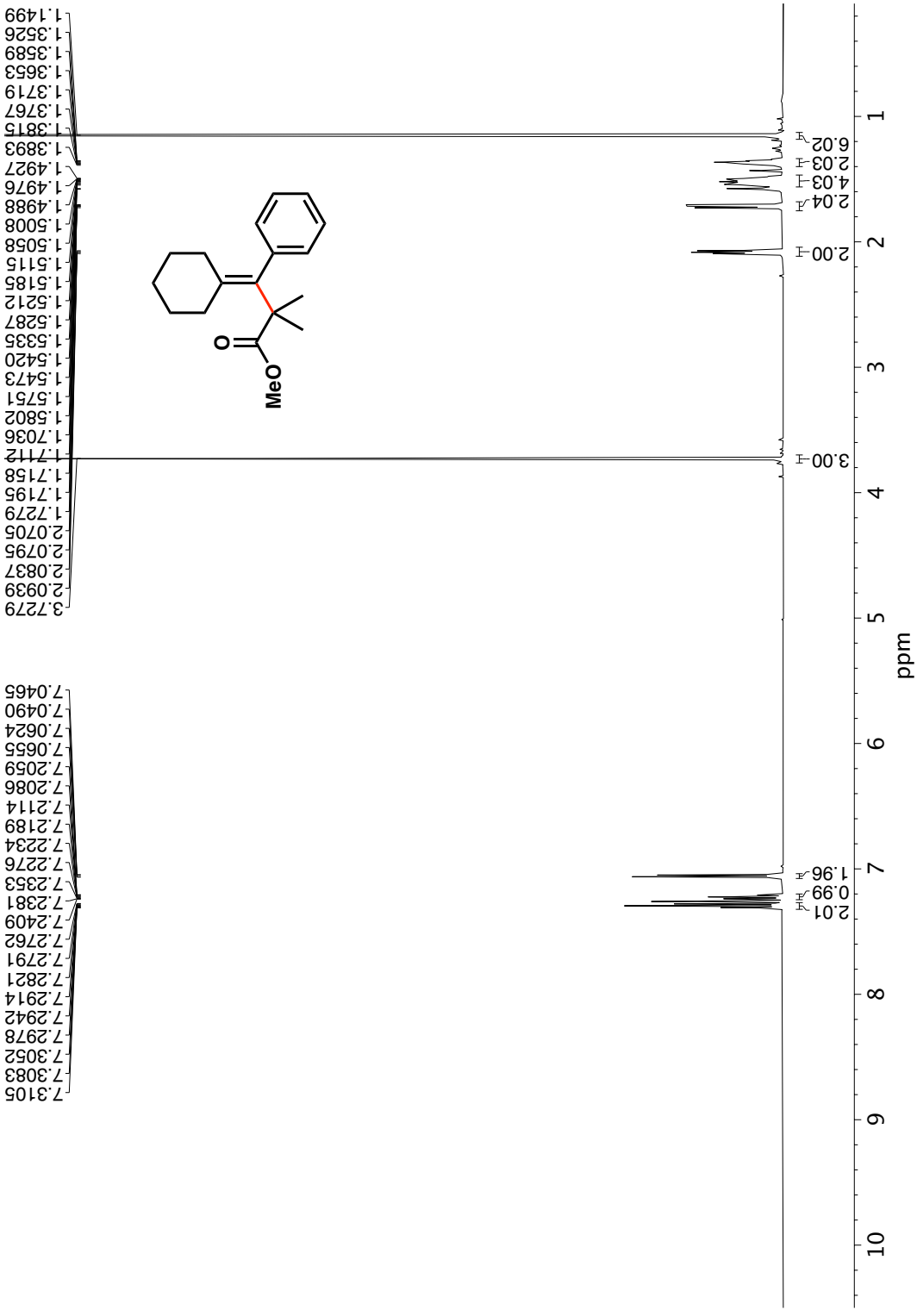
^{13}C NMR (126 MHz, $CDCl_3$) of compound **119f.**



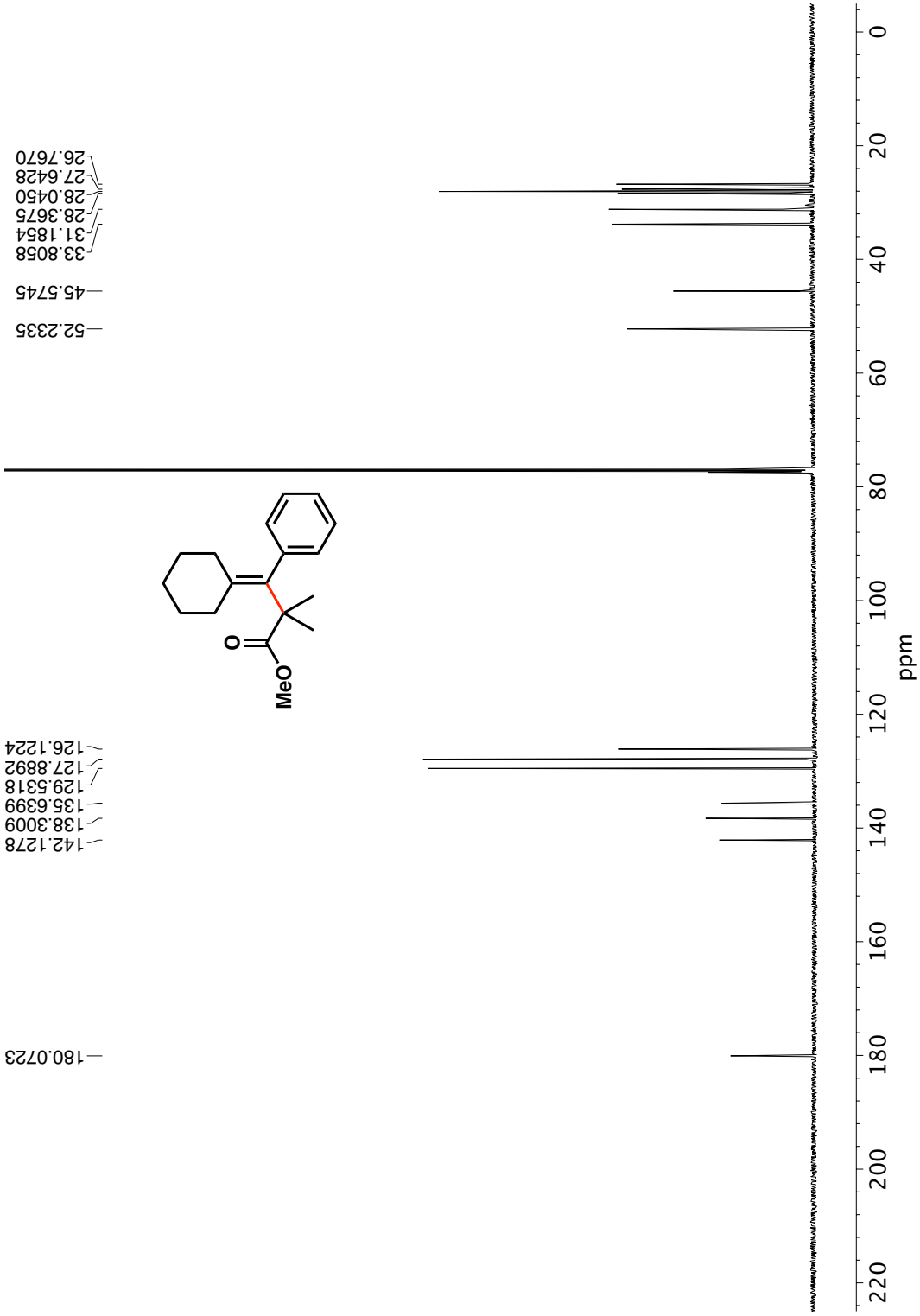
^{1}H NMR (400 MHz, $CDCl_3$) of compound **119g**.



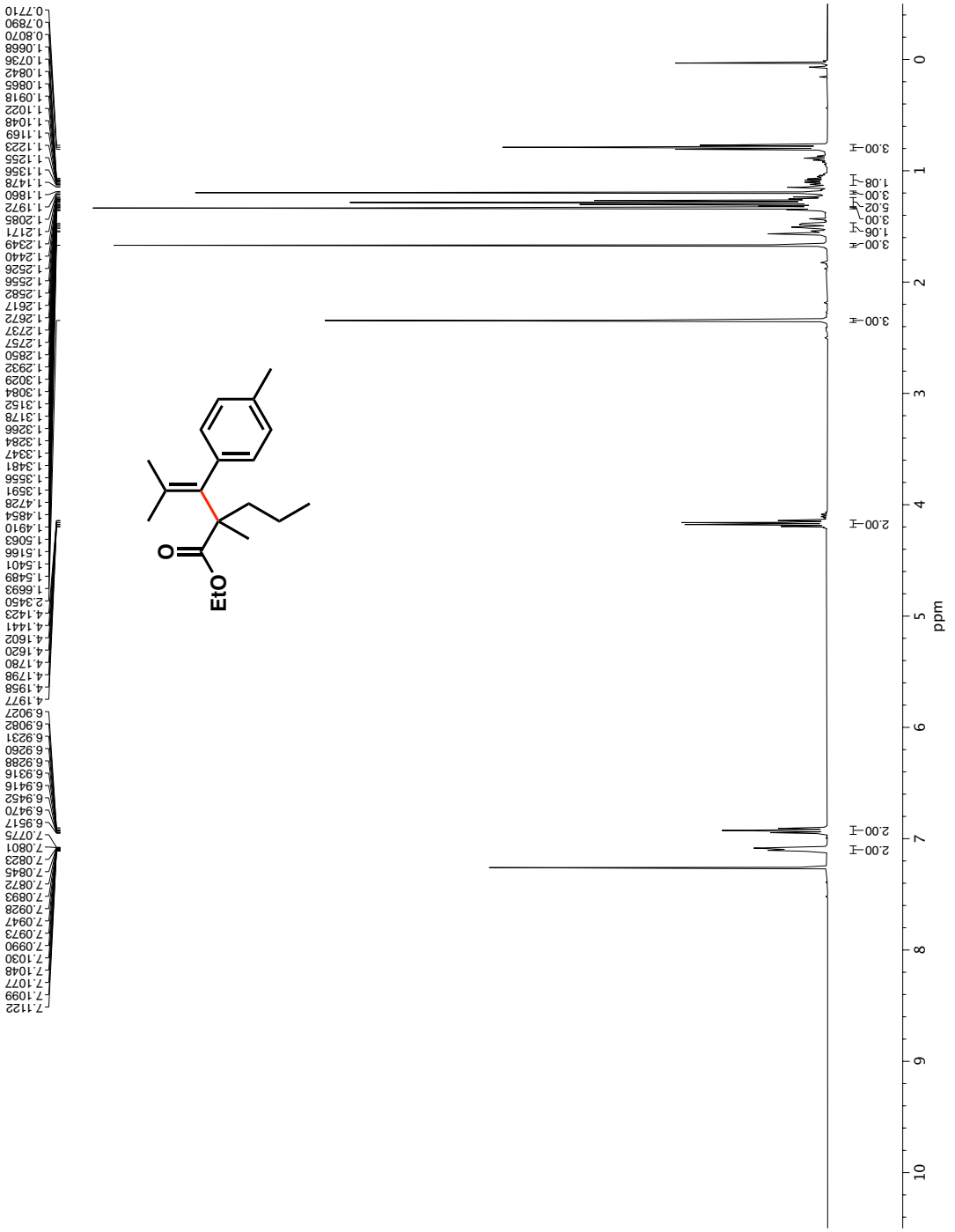
^{13}C NMR (101 MHz, $CDCl_3$) of compound **119g**.



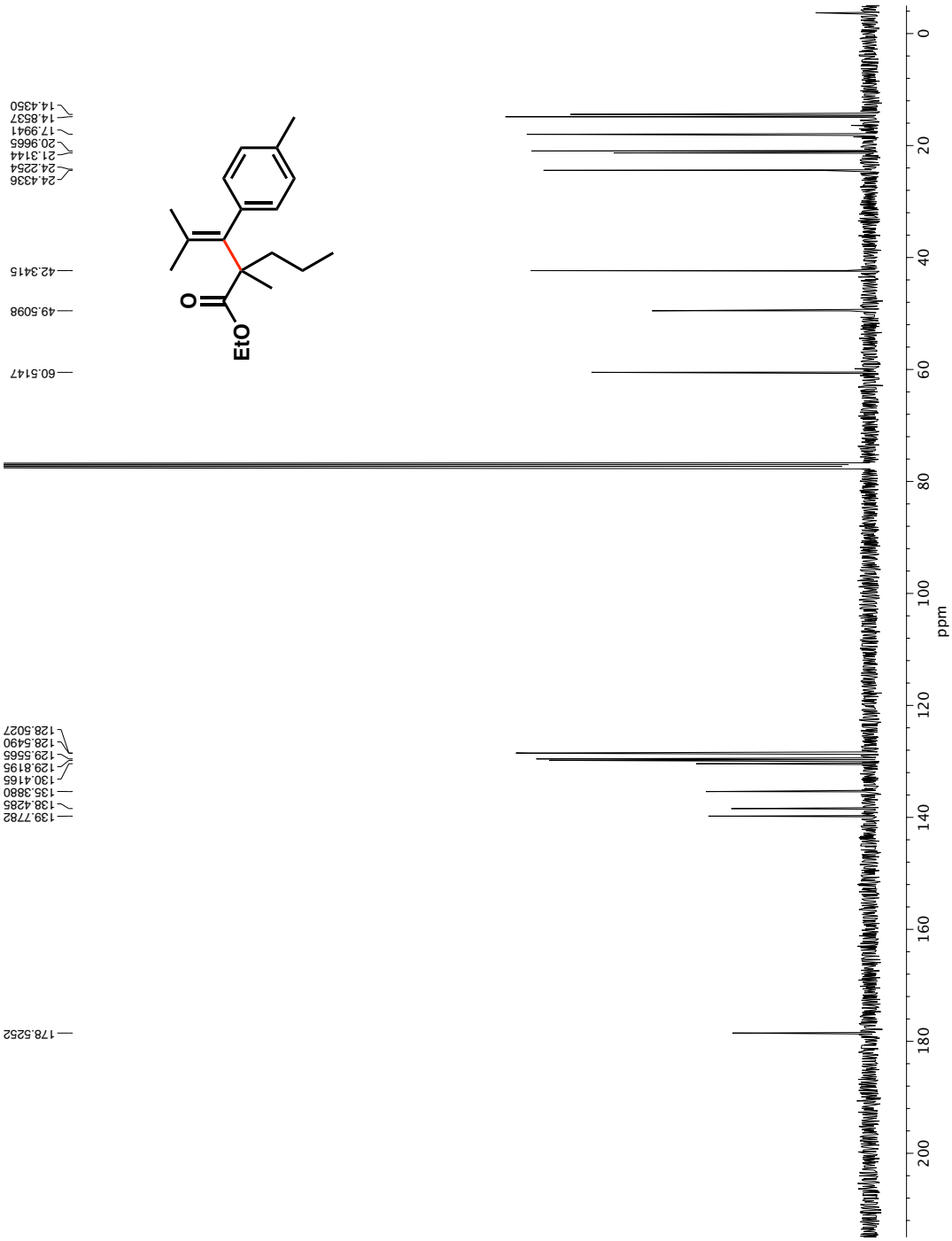
^{1}H NMR (300 MHz, $CDCl_3$) of compound **122a.**



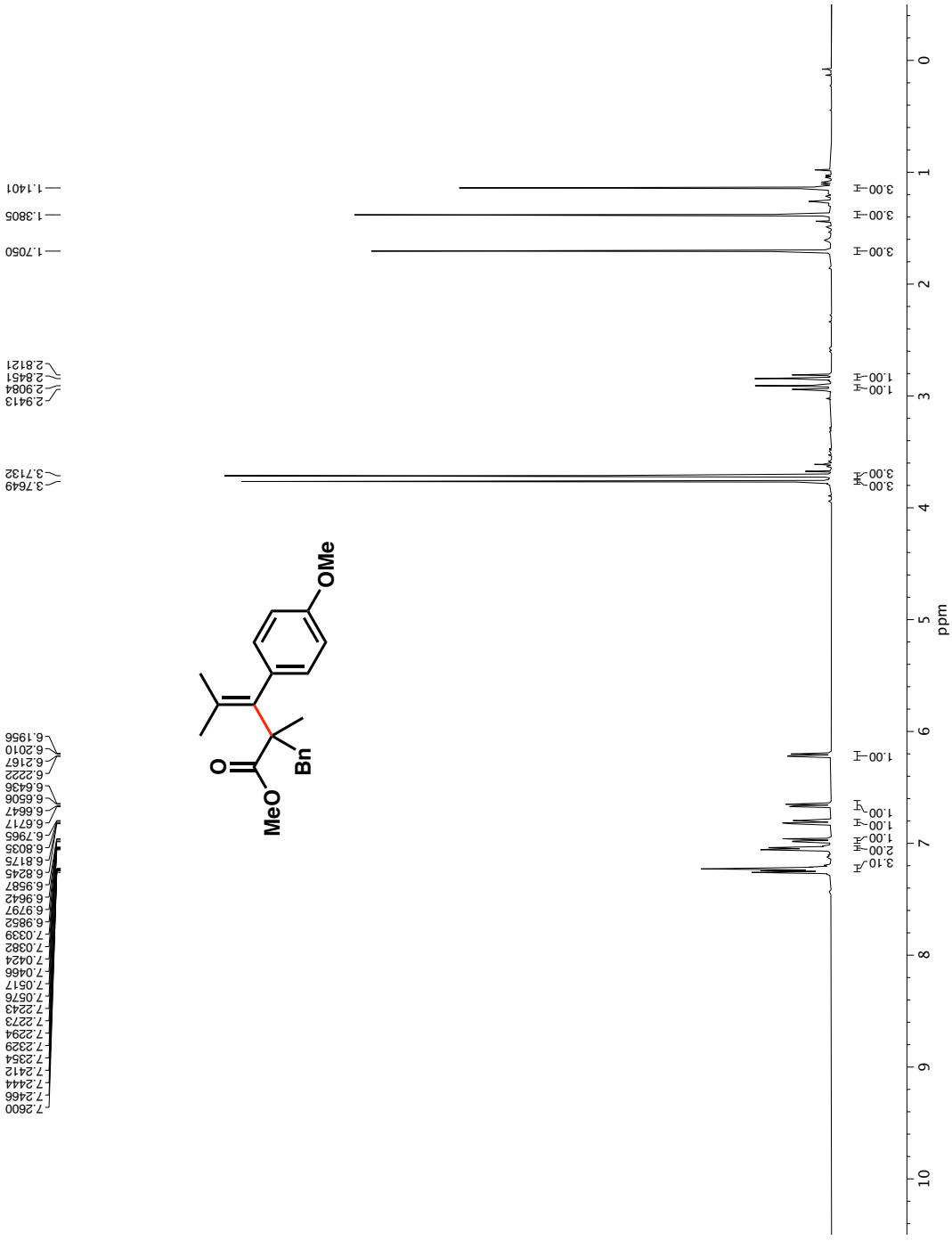
^{1}H NMR (500 MHz, $CDCl_3$) of compound **122a.**



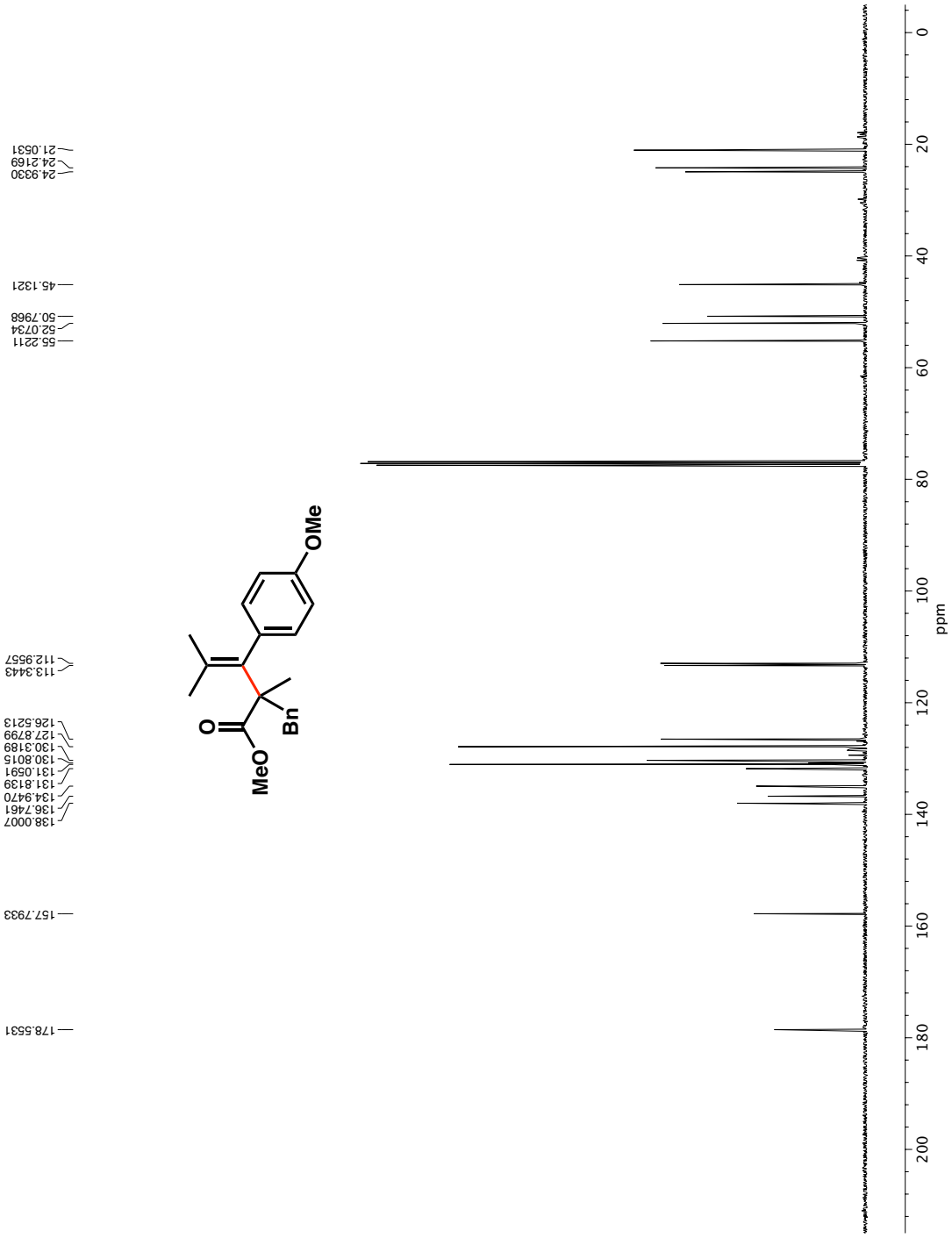
^{1}H NMR (400 MHz, $CDCl_3$) of compound **122b**.



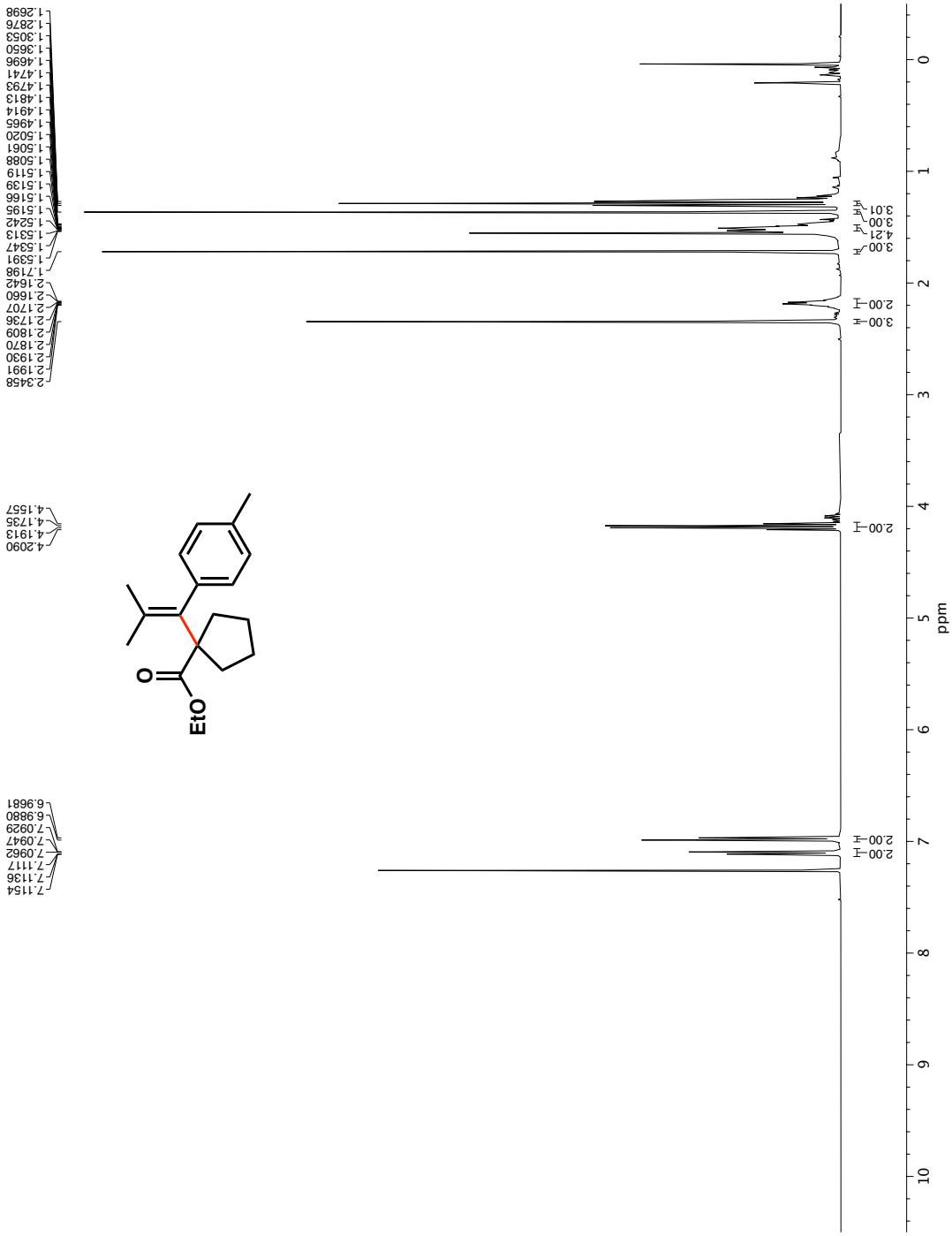
^{13}C NMR (101 MHz, $CDCl_3$) of compound **122b.**



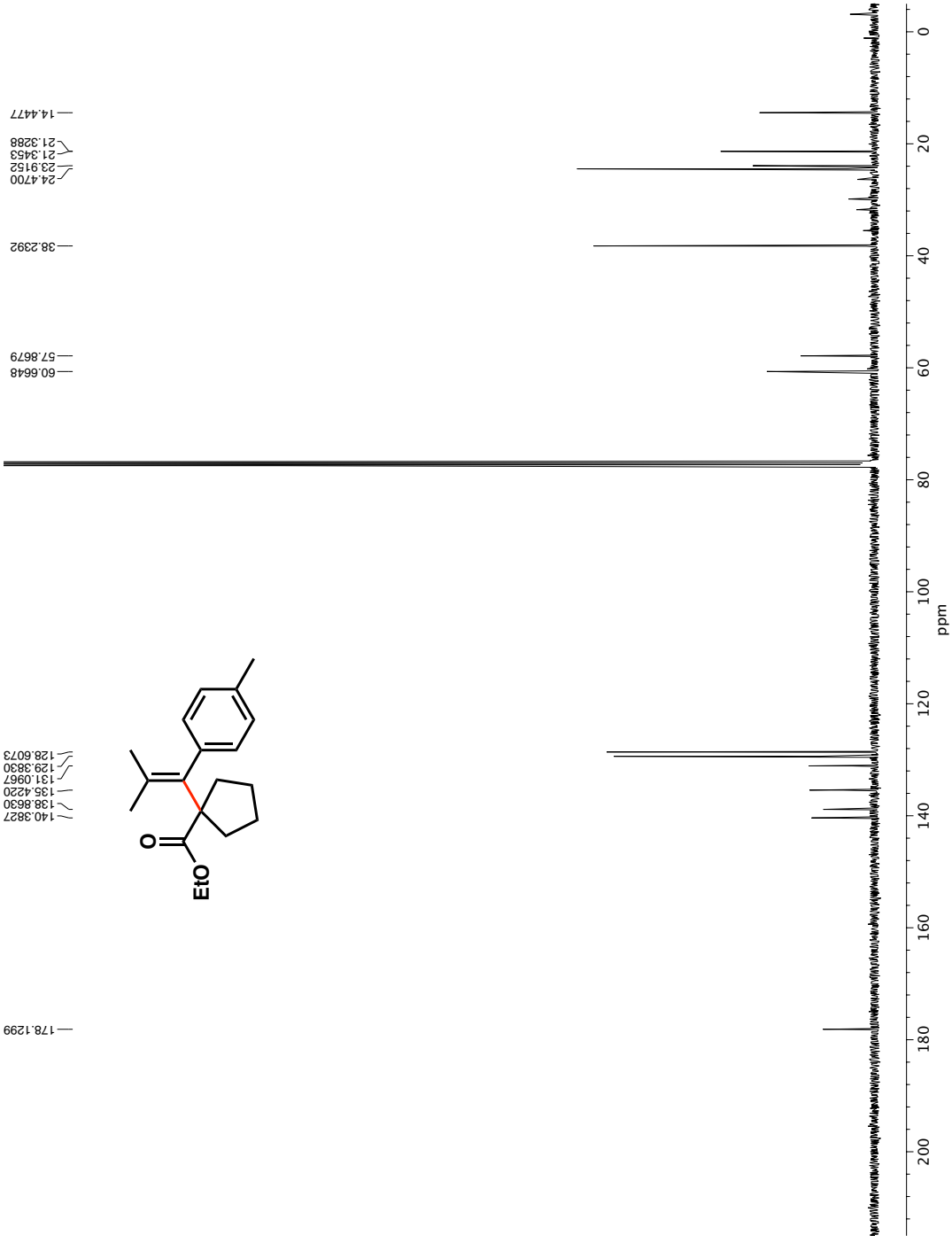
^{1}H NMR (400 MHz, $CDCl_3$) of compound **122c**.



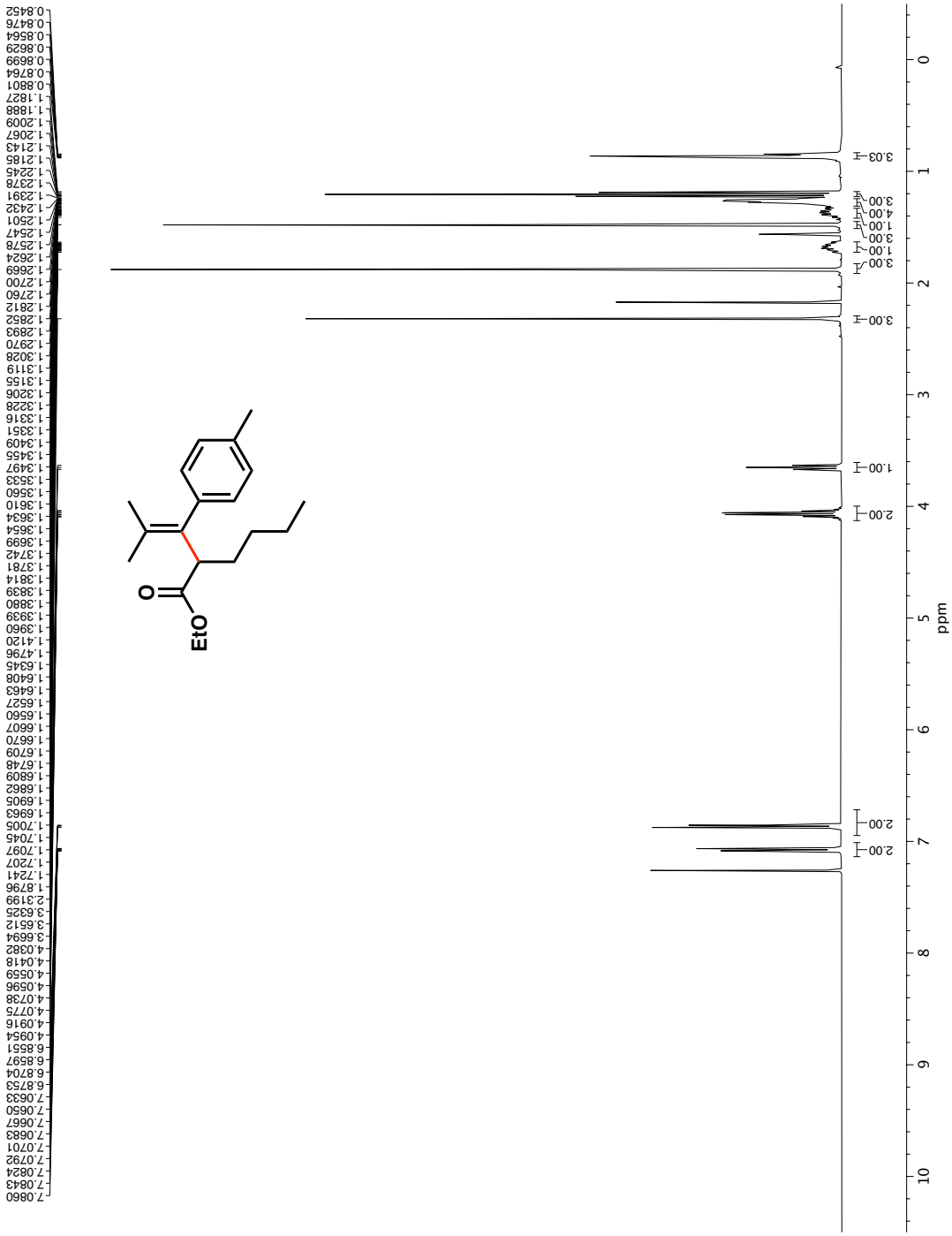
^{13}C NMR (400 MHz, $CDCl_3$) of compound **122c**.



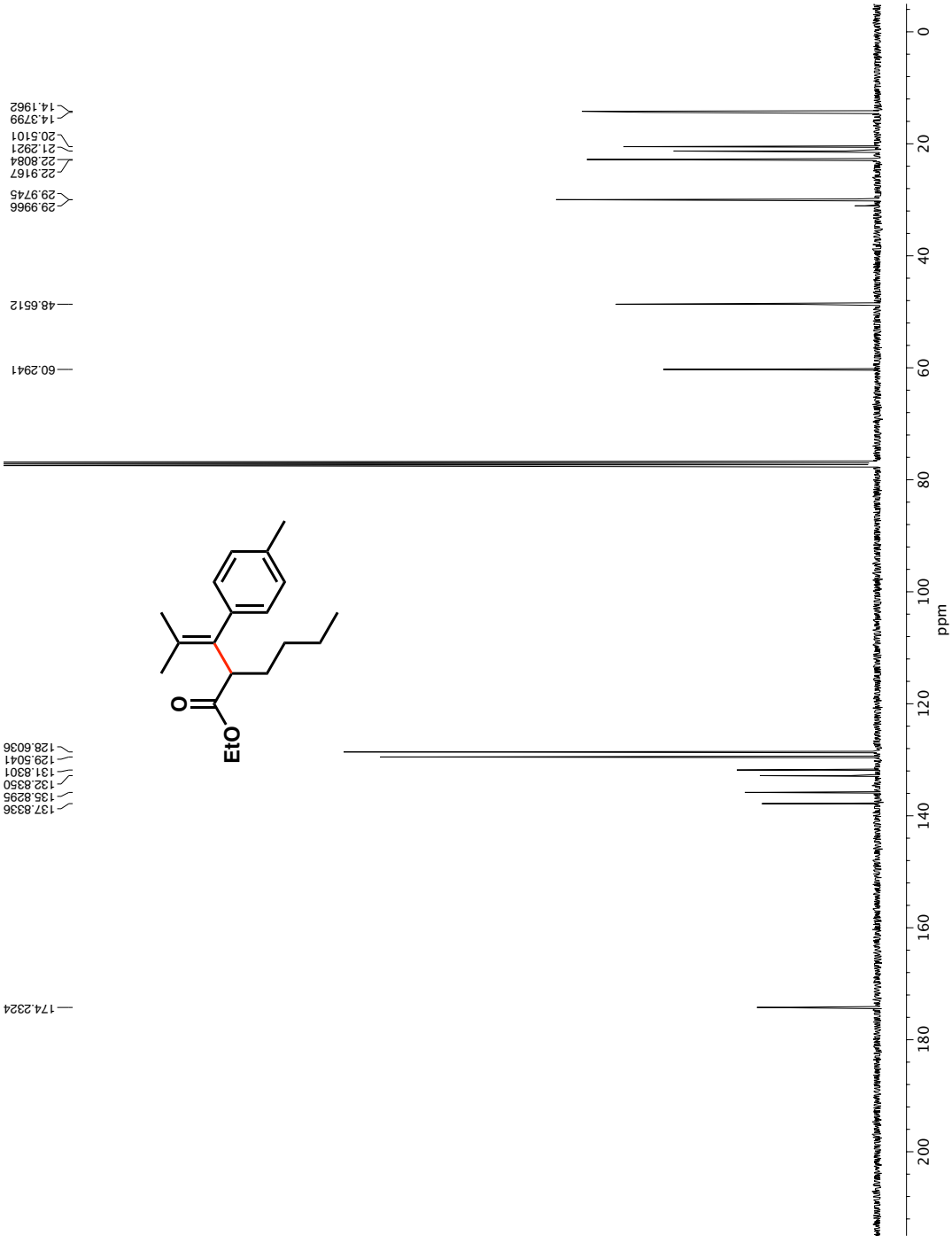
^{1}H NMR (400 MHz, $CDCl_3$) of compound **122d**.



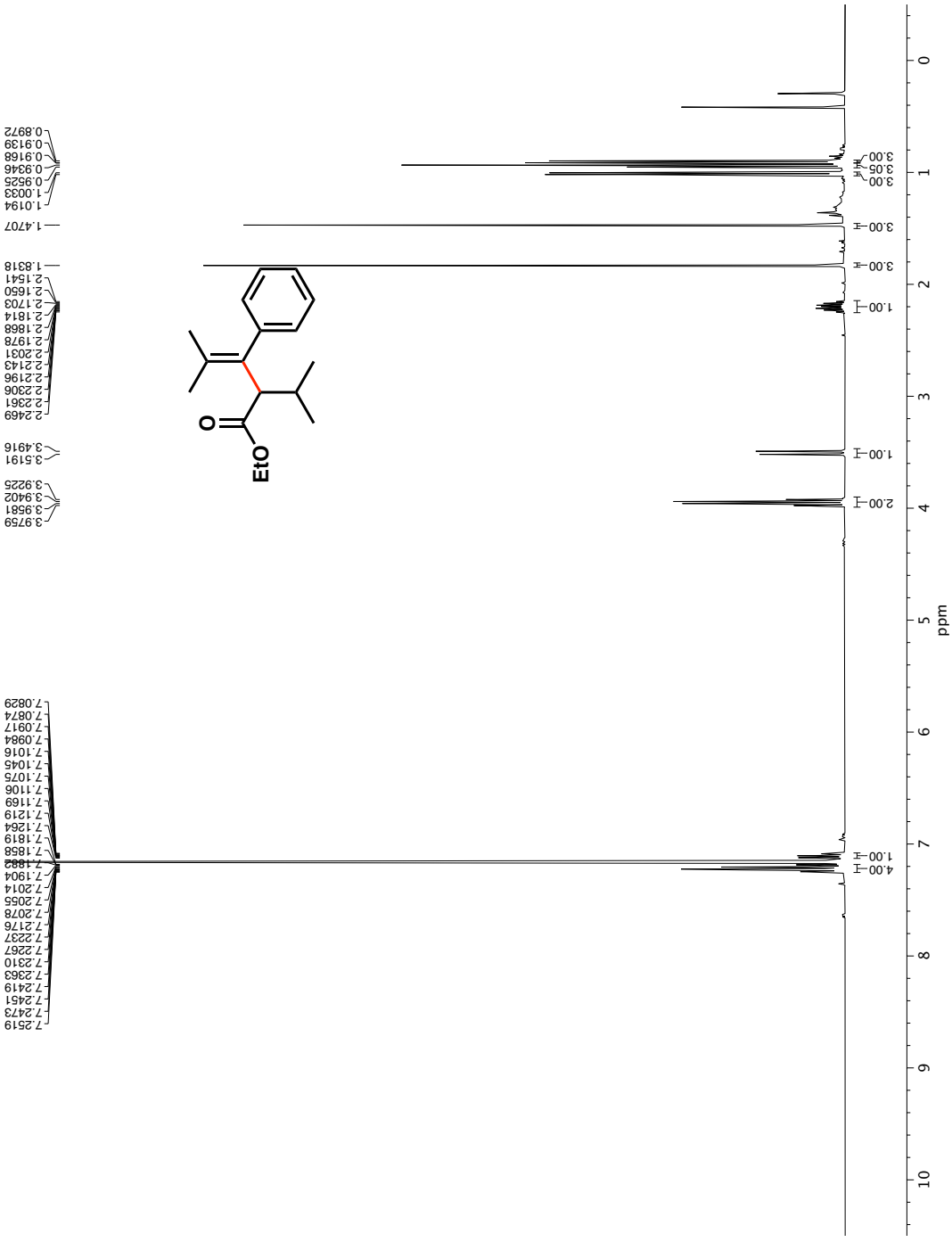
^{13}C NMR (101 MHz, $CDCl_3$) of compound **122d**.



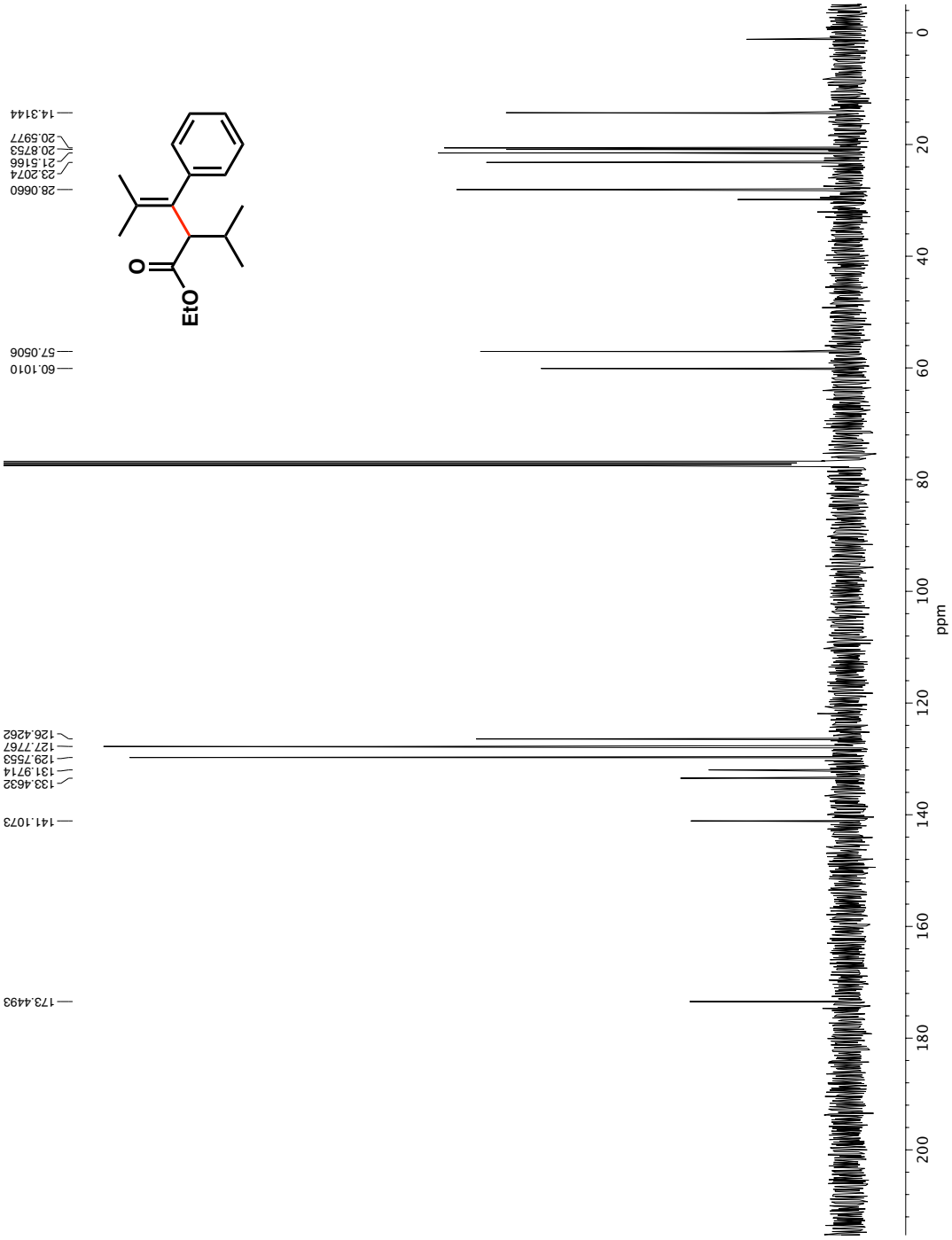
^{1}H NMR (400 MHz, $CDCl_3$) of compound **122e.**



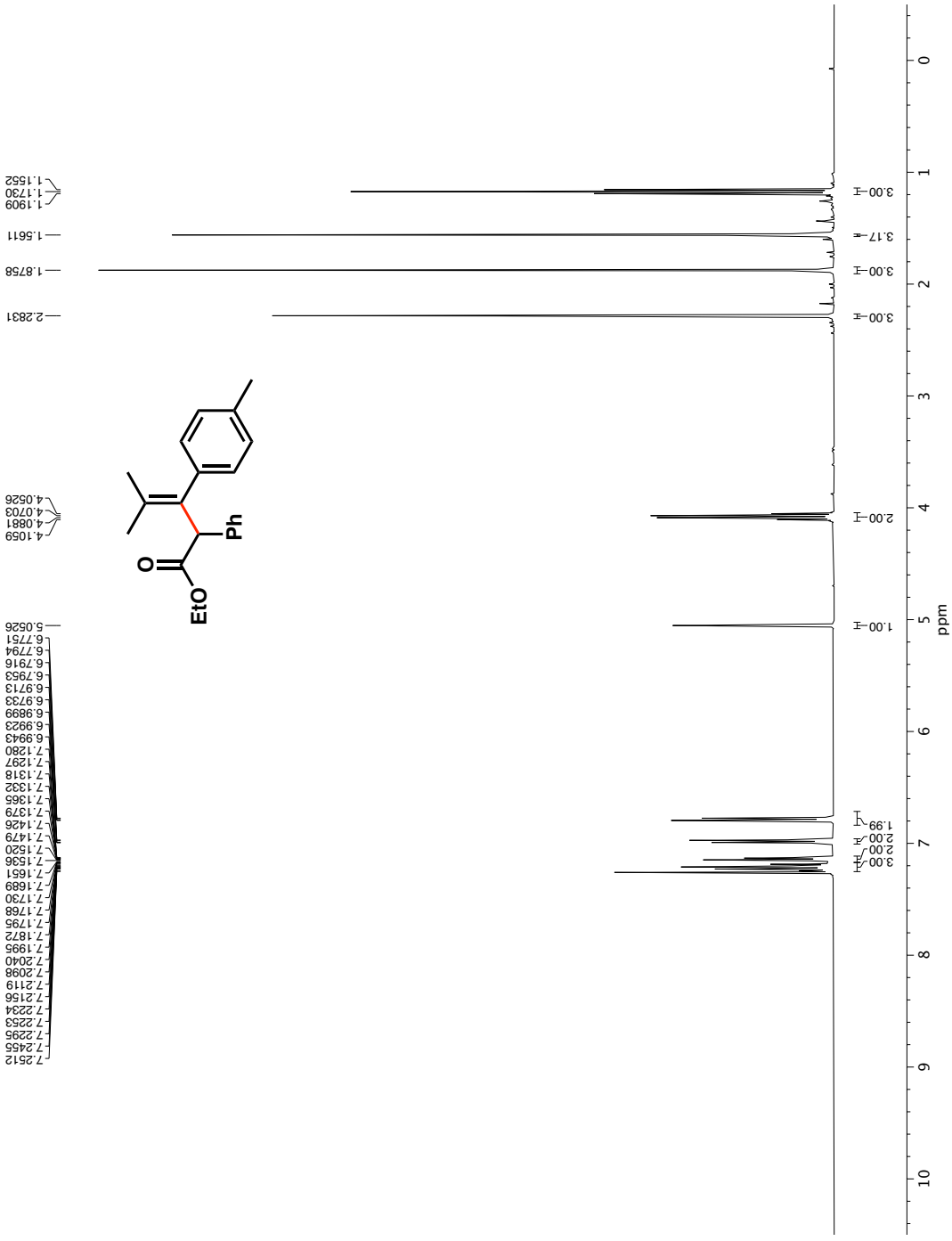
^{13}C NMR (101 MHz, $CDCl_3$) of compound **122e**.



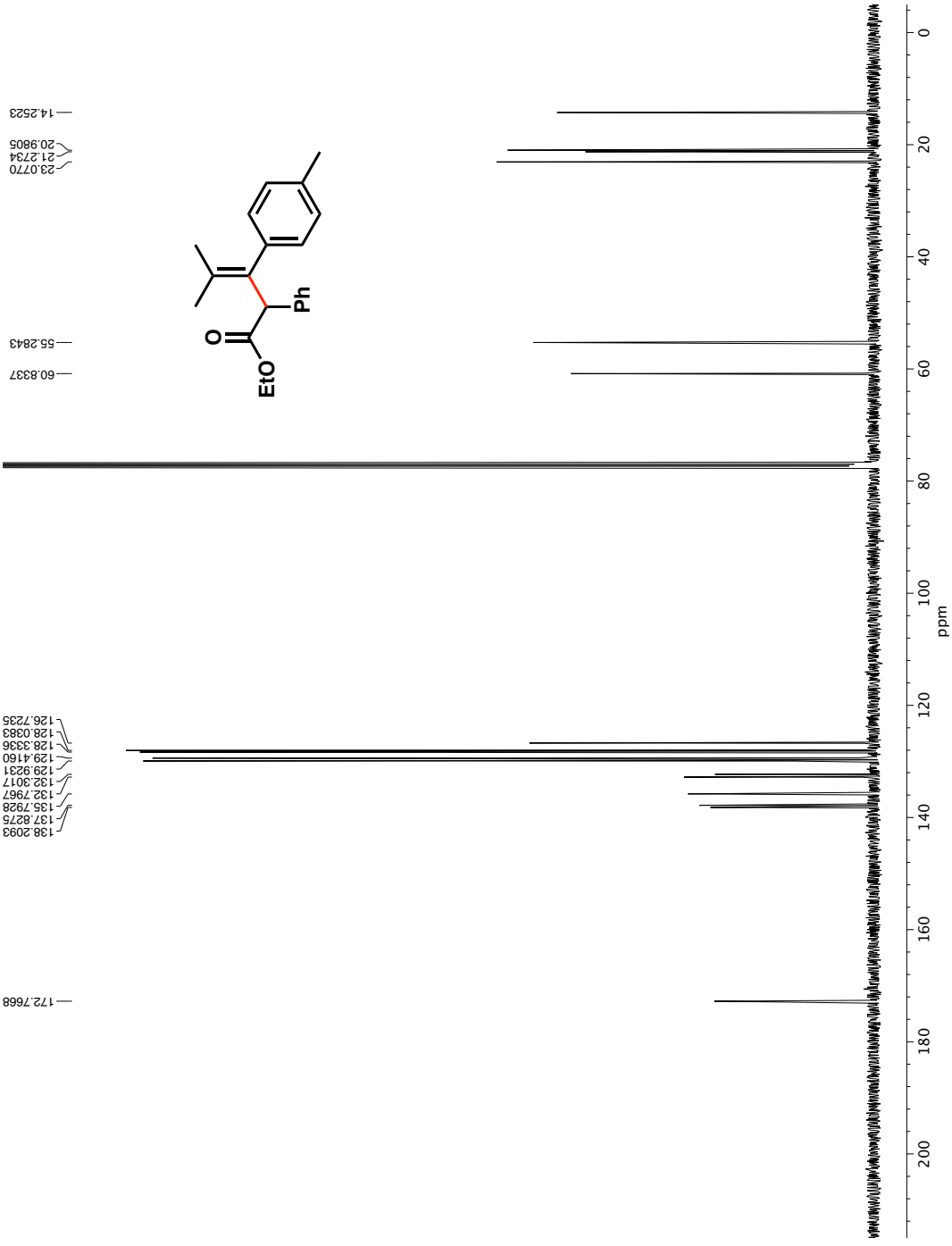
^{1}H NMR (400 MHz, C_6D_6) of compound **122f.**



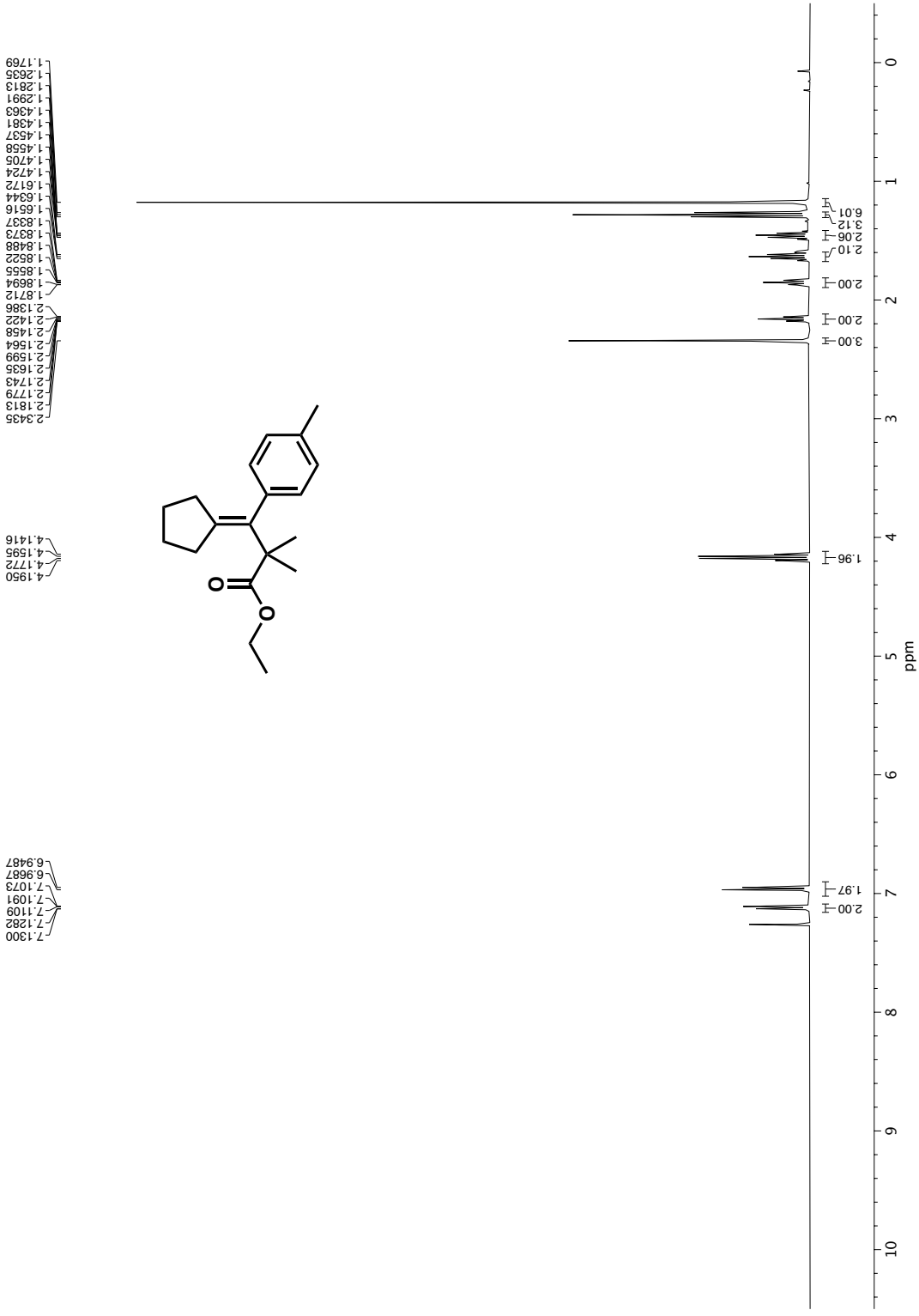
^{13}C NMR (101 MHz, $CDCl_3$) of compound **122f**.



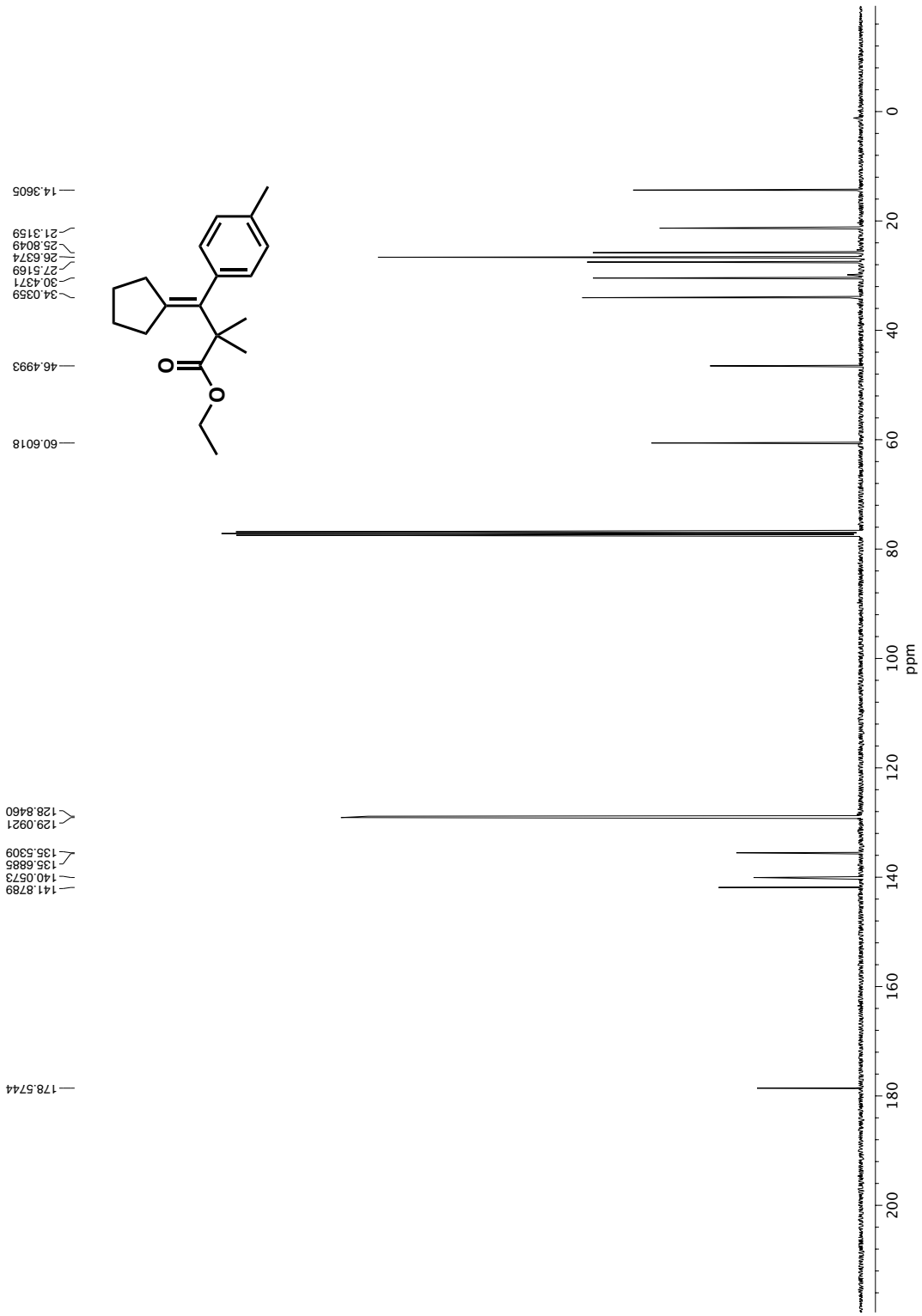
^{1}H NMR (400 MHz, $CDCl_3$) of compound **122g**.



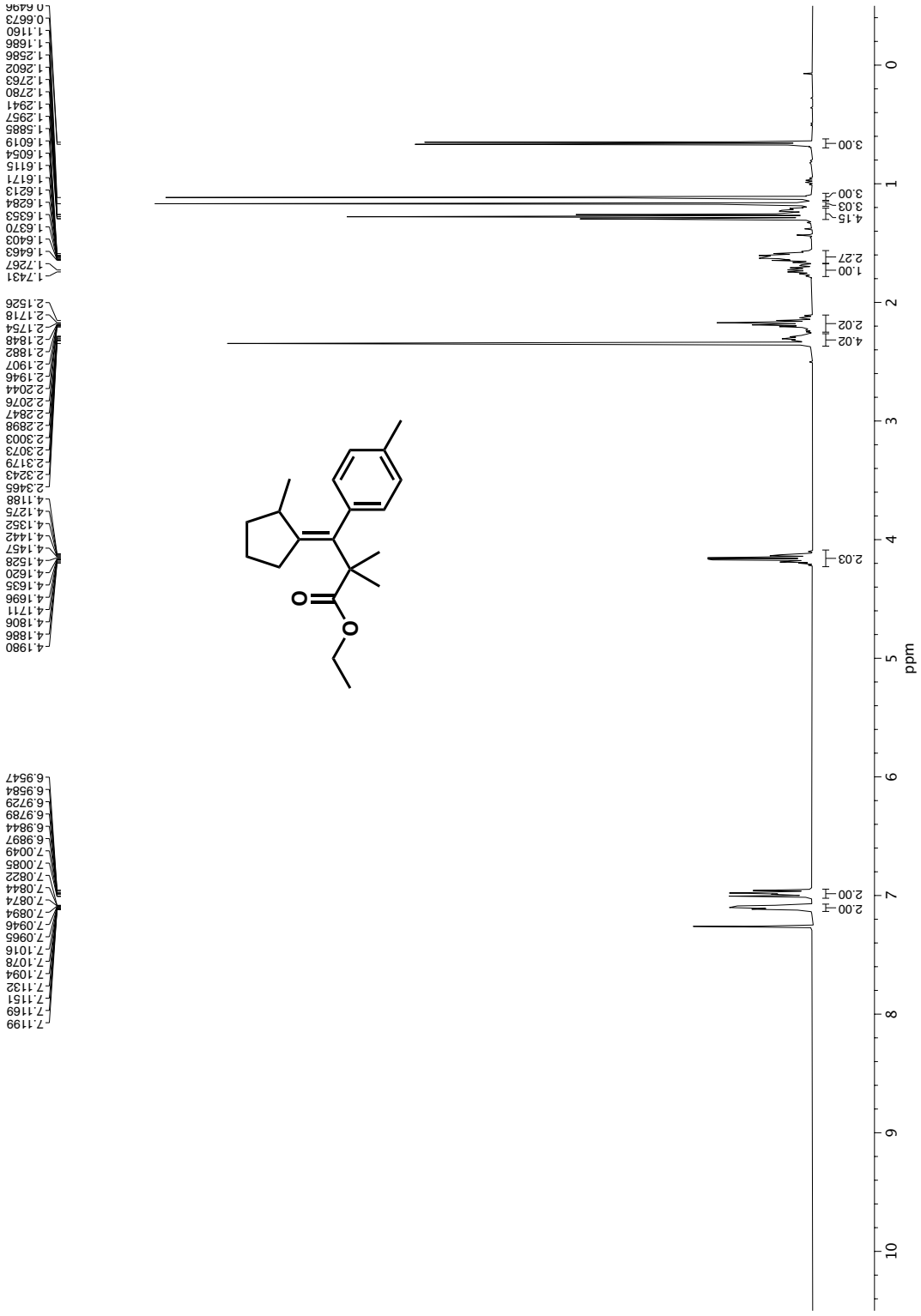
^{13}C NMR (400 MHz, $CDCl_3$) of compound **122g**.



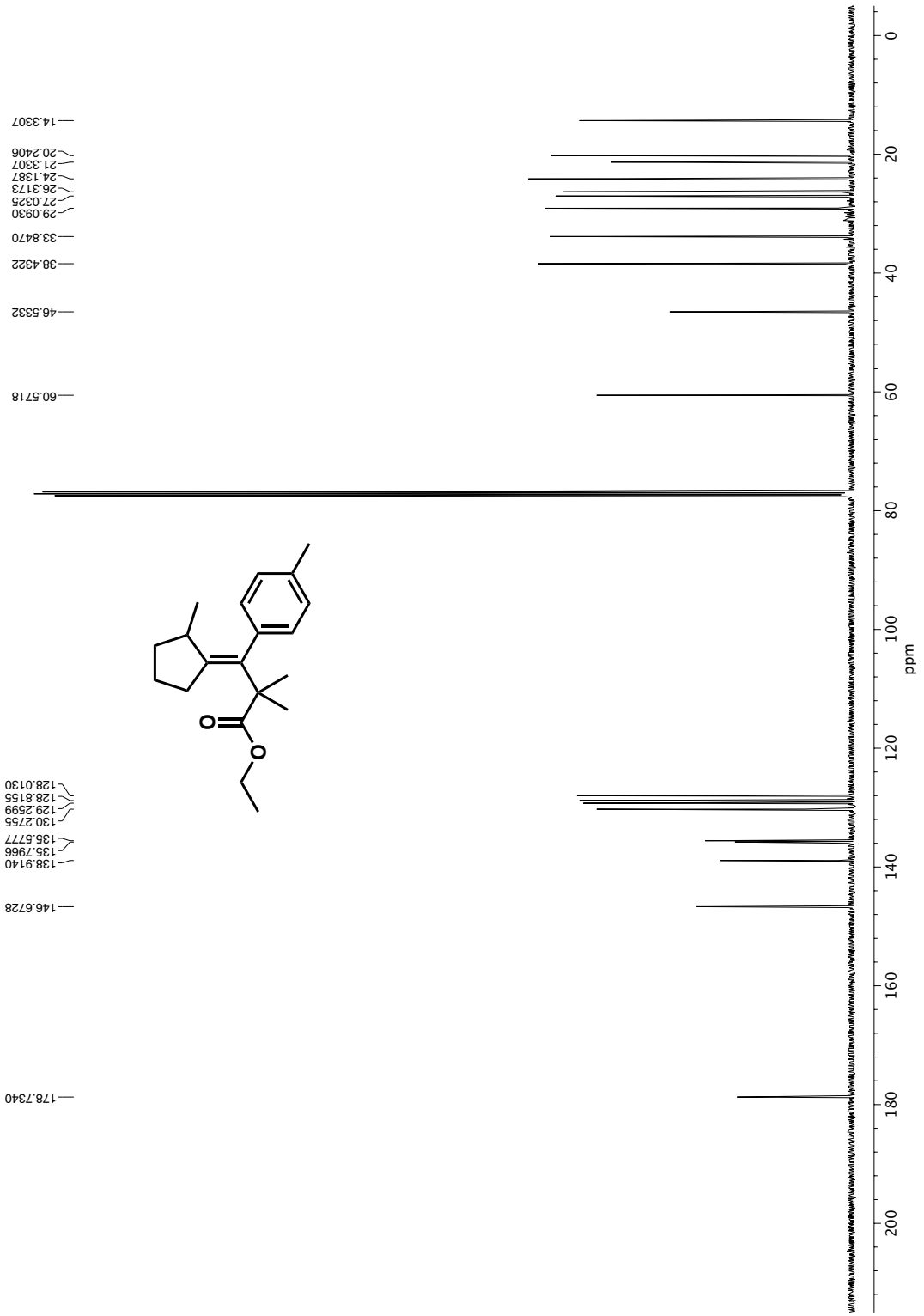
^{1}H NMR (400 MHz, $CDCl_3$) of compound **131a.**



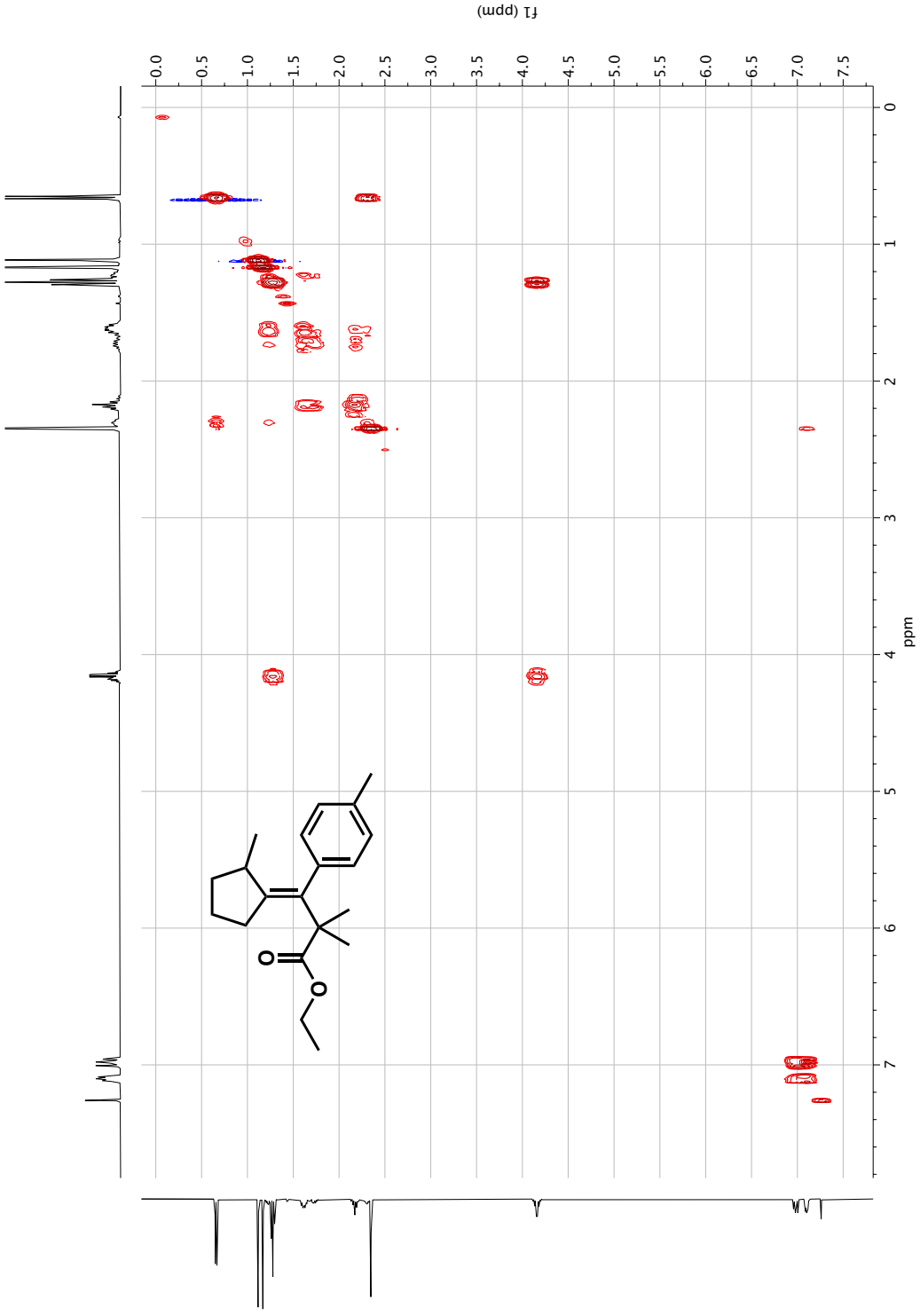
^{13}C NMR (101 MHz, $CDCl_3$) of compound **131a.**



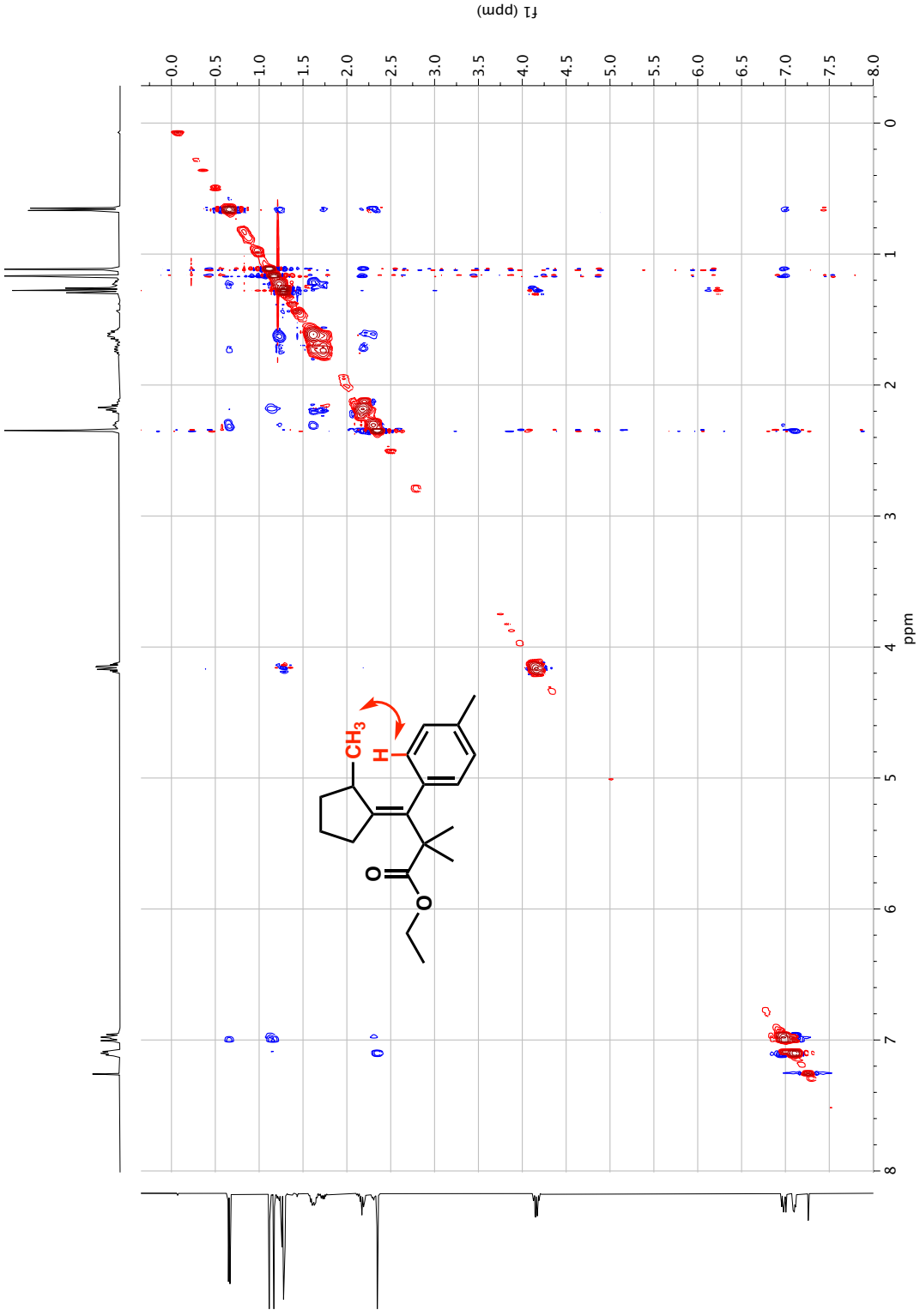
^{1}H NMR (400 MHz, $CDCl_3$) of compound **131b**.



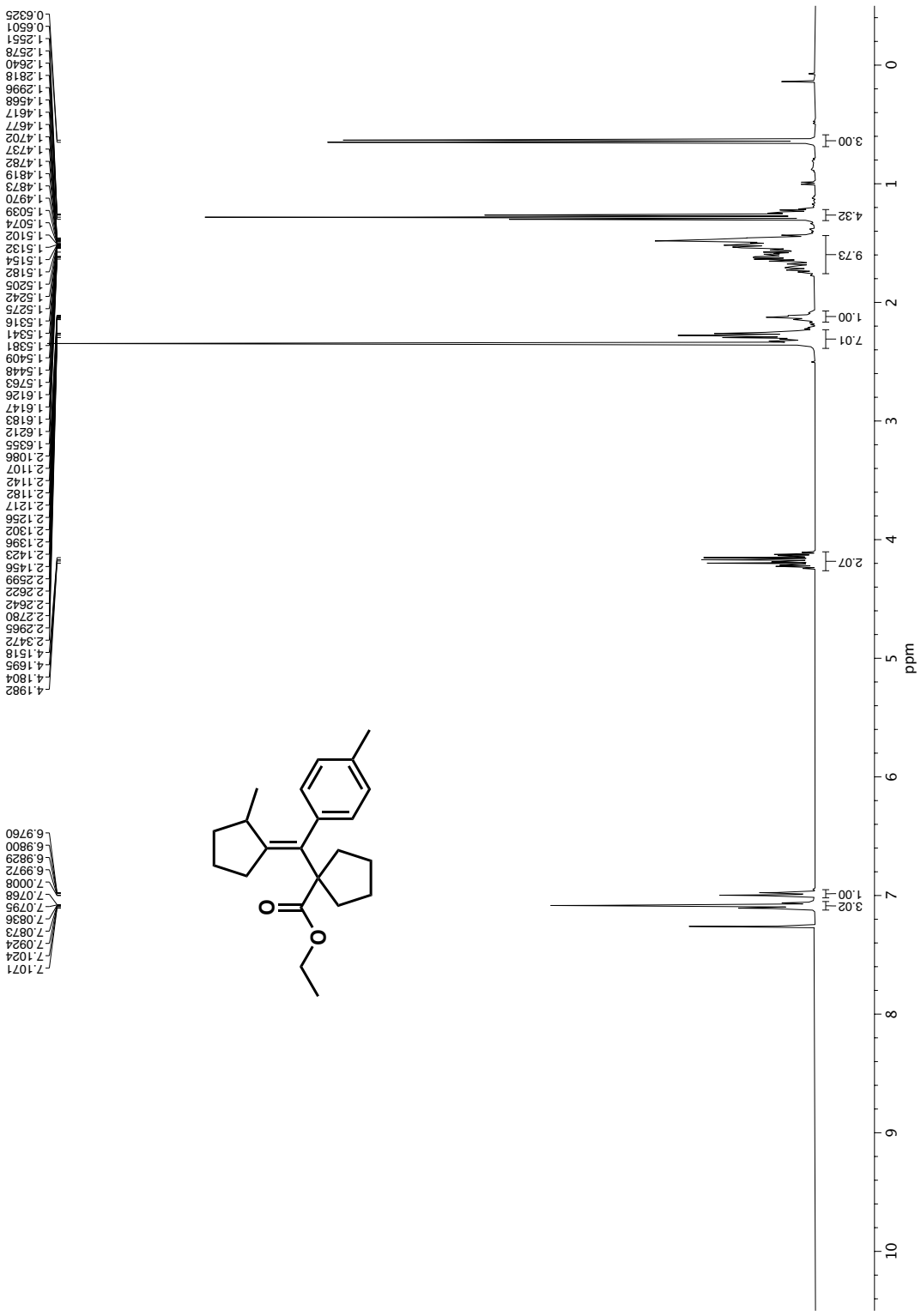
^{13}C NMR (101 MHz, $CDCl_3$) of compound **131b**.



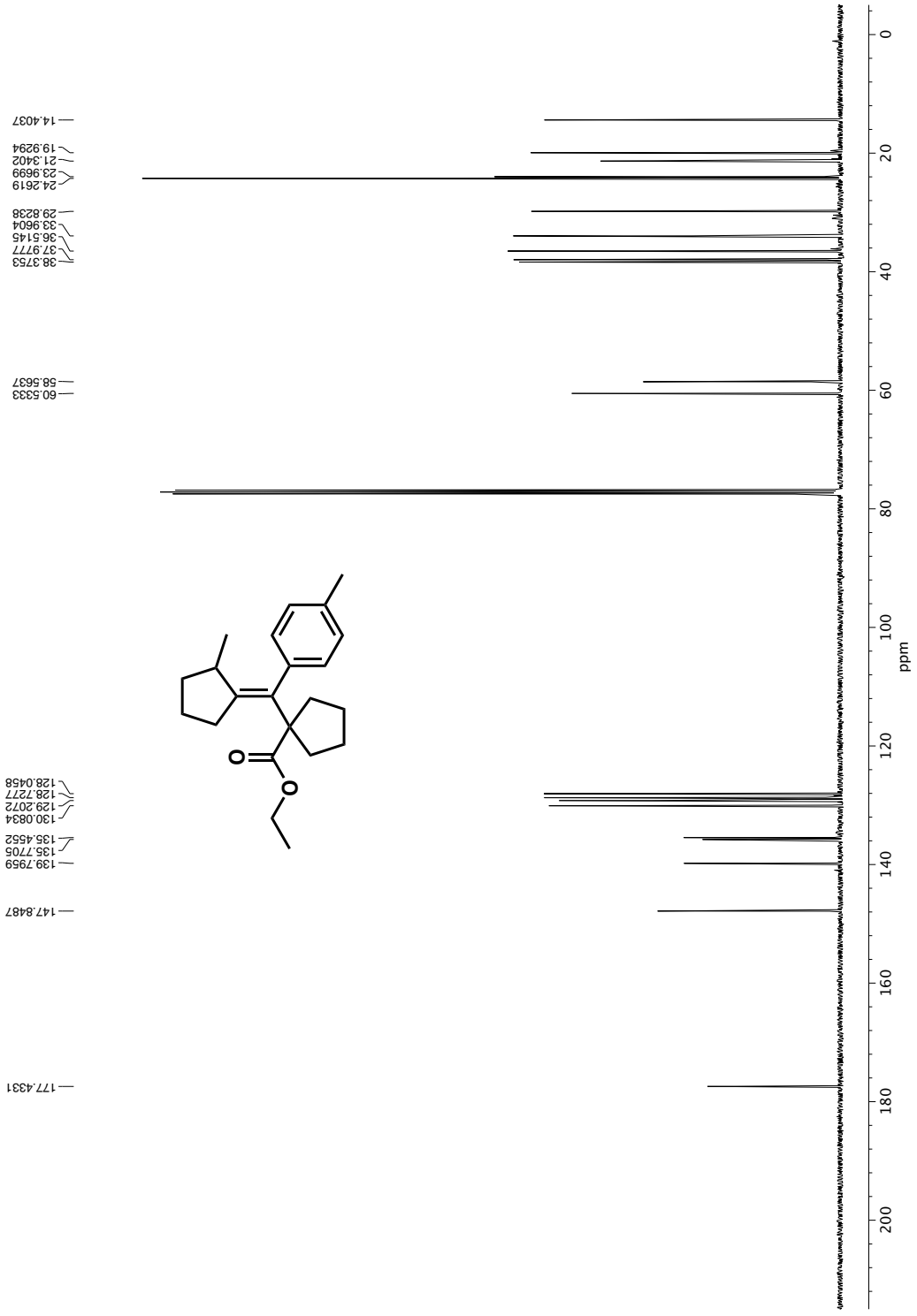
COSY NMR (400 MHz, $CDCl_3$) of **131b**.



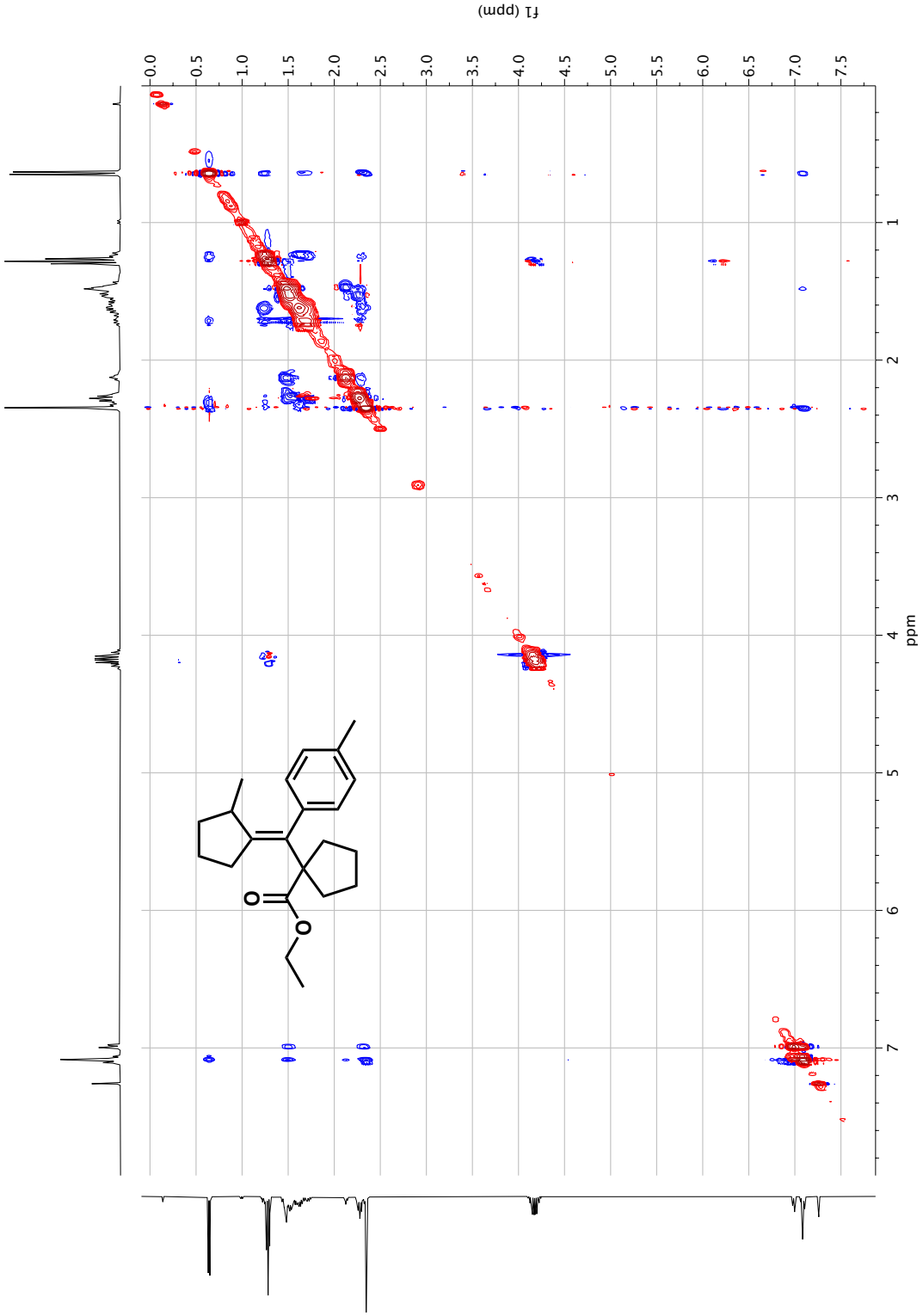
NOESY NMR (400 MHz, $CDCl_3$) of **131b.**



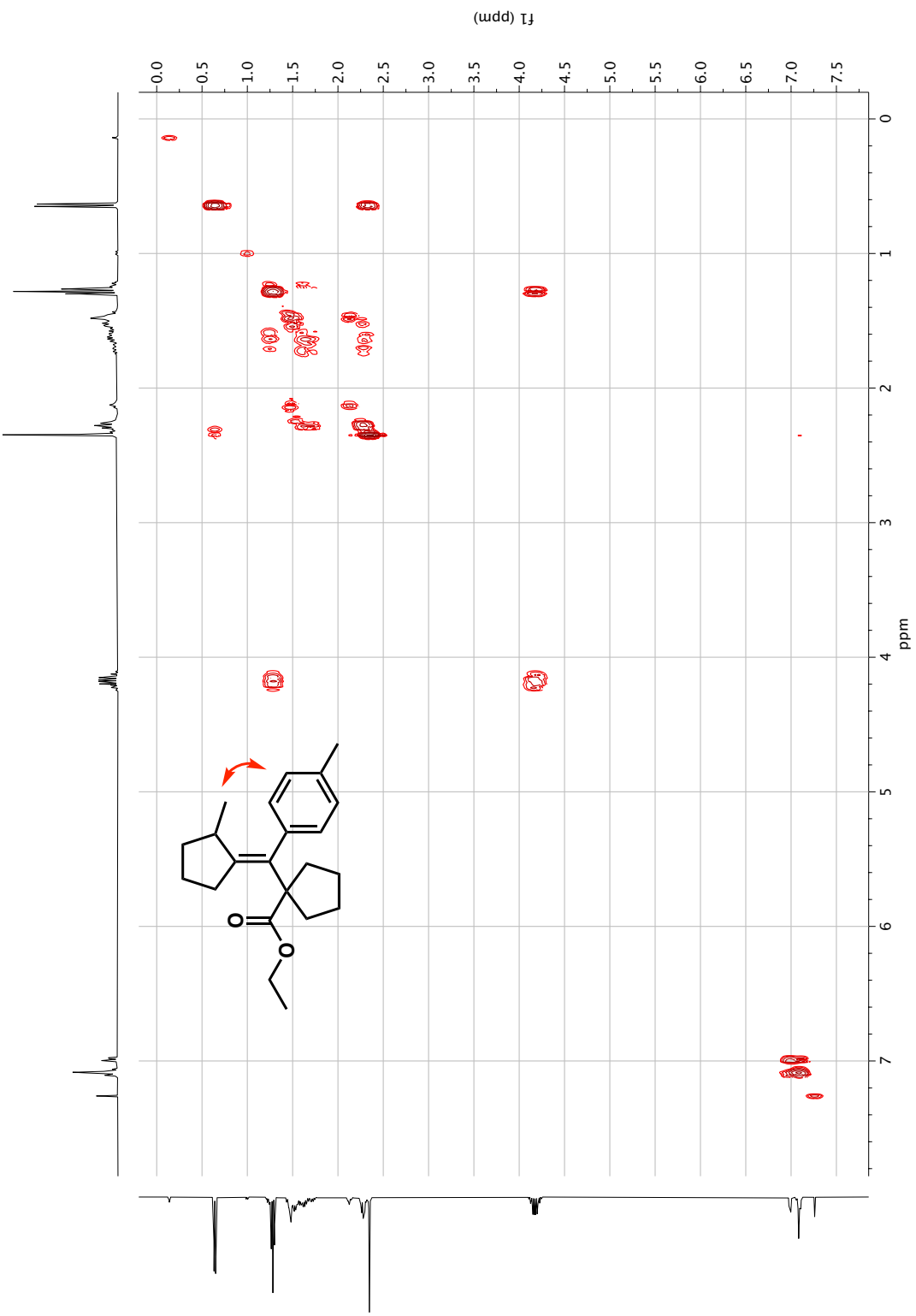
^{1}H NMR (400 MHz, $CDCl_3$) of compound **131c.**



^{13}C NMR (101 MHz, $CDCl_3$) of compound **131c.**



COSY NMR (400 MHz, $CDCl_3$) of compound **131c.**



NOESY NMR (400 MHz, $CDCl_3$) of compound **131c.**

Chapter 3

Cationic Claisen-Type Cascade Reactions Enabled by Vinyl Cation Capture[†]

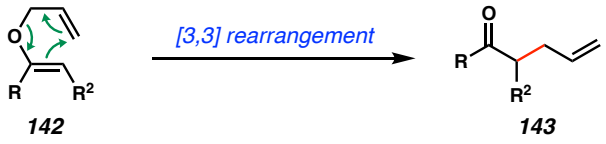
3.1 INTRODUCTION

Since its discovery in the early 1900s, the Claisen rearrangement of allyl vinyl ethers (**142**) to access α-allylated ketone products (**143**) has earned considerable attention due to its synthetic utility and intriguing mechanism (Scheme 3.1).[1–3] One of the challenges associated with the classical Claisen rearrangement is the synthesis of the requisite allyl vinyl ether. Enolate alkylation can be problematic due to unselective O- *vs*. C-alkylation, and the potential for generating *E/Z* olefin isomers, which challenge selective product formation.[4,5] Other strategies involve olefin isomerization[6–13], leaving group elimination[14], C–O cross coupling[15–18], alkyne hydroalkoxylation[19,20], carbonyl alkenylation[21–26], and

[†] This research was performed in collaboration with Sepand K. Nistanaki, Woojin Lee, and Krista Dong.

metal-catalyzed vinyl ether exchange.[27–29]

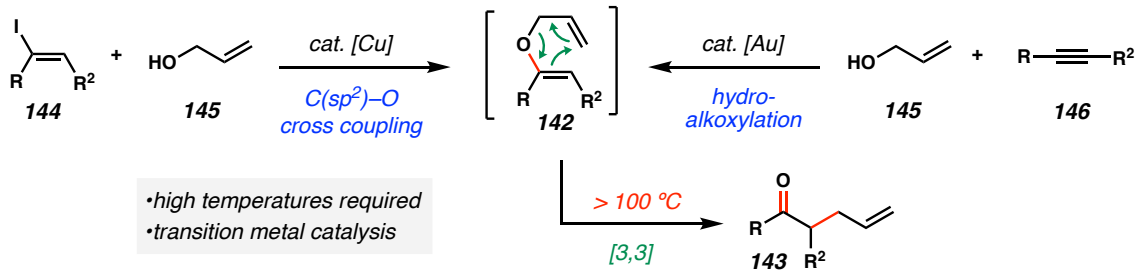
Scheme 3.1. *Claisen rearrangement of allyl vinyl ethers and associated challenges.*



challenges of allyl vinyl ethers synthesis:
•unselective O- vs. C-alkylation
•E/Z olefin isomer selectivity
•challenging isolation due to ether instability

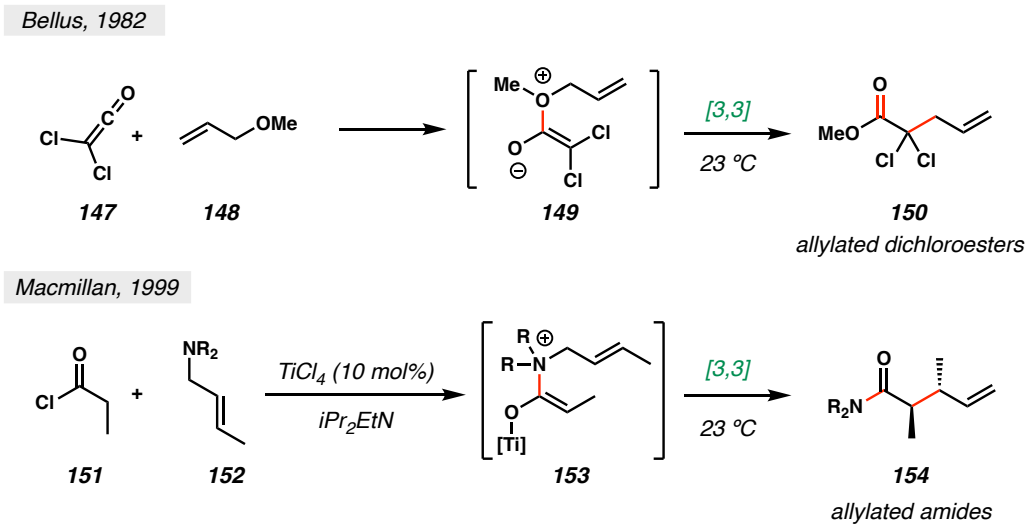
Methods for the *in-situ* generation and subsequent direct [3,3] rearrangement of allyl vinyl ethers eliminates the need for vinyl ether isolation (which can be unstable under acidic conditions),[30,31] and offers an attractive strategy to rapidly generate complexity from simple reaction partners. Such an approach has been applied to several transition metal-catalyzed reactions, such as Buchwald's Cu-catalyzed C(sp^2)–O cross coupling of vinyl iodides (**144**) with allyl alcohols (**145**) to form allyl vinyl ether **142** *in-situ*, which can then subsequently rearrange to the product (**143**) under the reaction conditions at elevated temperatures (Scheme 3.2).[32] Another approach includes Au-catalyzed hydroalkoxylation of alkynes (**146**) to again access **142** in-situ.[33–35] Other approaches include Pd-catalyzed vinyl ether exchange[36] and Rh-catalyzed elimination[37] and O–H insertion of diazo compounds.[38] While these reports demonstrate the synthetic utility of intermolecular Claisen cascade reactions, they require transition metal catalysts and high reaction temperatures to affect the thermal [3,3] rearrangement of unactivated substrates.

Scheme 3.2. *Claisen cascade reactions via transition metal catalysis.*



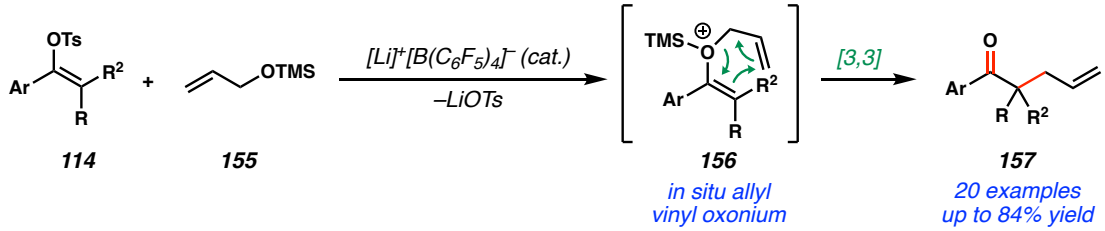
An alternative approach stems from Bellus and co-workers' report that highly electrophilic dichloroketenes (**147**) can be trapped by allyl ethers (**148**) to form zwitterionic intermediates (**149**) that undergo fast [3,3] sigmatropic rearrangement to form allylated dichloresters **150** (Scheme 3.3).[39–41] MacMillan and Nubbemeyer have expanded on this work by demonstrating that simpler acyl chlorides (**151**) could similarly engage allylamines (**152**) *via* Lewis acid catalysis, wherein a charged intermediate (**153**) undergoes rearrangement at room temperature to generate allylated amides (**154**) (Scheme 3.3).[42–44]

Scheme 3.3. *Charge-accelerated Claisen rearrangements via electrophile trapping.*



This aza-Claisen approach has been expanded to Lewis acid activation of allenoates[45] and additions to ketiminium ions[46,47], all of which have several attractive features including (1) the ability to couple two components in an intermolecular Claisen cascade reaction, and (2) an acceleration effect imparted by charge, enabling rearrangements to occur at significantly lower temperatures. However, these aza-Claisen type reactions are limited to specific products that could be accessed, largely predicted by the heteroatom-stabilized electrophile that can be generated. This ultimately challenges its application in more classical aliphatic Claisen rearrangements, which have found significant utility in synthetic chemistry.

Scheme 3.4. *This work: cationic Claisen cascade via main group catalysis.*



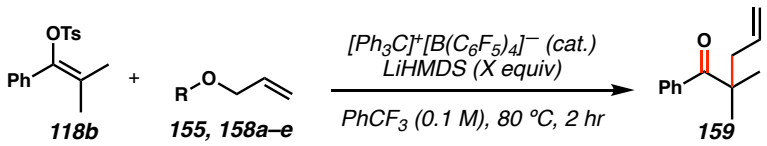
Inspired by the ability to generate allyl vinyl ethers through transition metal-catalyzed cross coupling reactions and the documented accelerating effects of charge in sigmatropic rearrangements[39,42,47–51], we envisioned a strategy that could merge the two in a transition metal-free catalytic platform. We hypothesized that generation of a high energy vinyl carbocation through ionization of vinyl tosylates (**114**) would precede reaction with weakly nucleophilic allyl ethers (**155**) to generate a vinyl oxonium cation (**156**) poised to undergo a charge-accelerated [3,3] sigmatropic rearrangement to form α-allylated ketones

(**157**) (Scheme 3.4). Ultimately, this unites two readily accessible starting materials, as vinyl tosylates are derived from simple ketones and allyl ethers are easily synthesized.

3.2 REACTION OPTIMIZATION

Based on previous work utilizing Li^+ weakly coordinating anion (WCA) salts to ionize vinyl sulfonates[52], we began exploring the reactions of allyl ethers **158a** and **158b** with vinyl tosylate **118a** in the presence of commercially-available $[Ph_3C]^+[B(C_6F_5)_4]^-$, which generates Lewis acidic $[Li]^+[B(C_6F_5)_4]^-$ in the presence of LiHMDS (Table 3.1). We initially found that ethyl allyl ether **158a** and diallyl ether **158b** in the presence of 10 mol% $[Ph_3C]^+[B(C_6F_5)_4]^-$ and stoichiometric LiHMDS furnished α-allylated ketone **159** after 2 hours of heating at 80 ºC, presumably arising from the proposed [3,3] rearrangement (Table 3.1, entries 1–2). However, full starting material consumption was not observed. Next, silyl allyl ethers (**155, 158c–e**) were surveyed. While sterically bulky silyl allyl ethers, such as triisoproyl (TIPS) (**158c**) resulted in no product despite full consumption of starting tosylate, less bulky *tert*-butyldimethylsilyl (TBS) allyl ether (**158d**) produced **159** in 41% yield (entries 3 and 4). Moving to even smaller triethylsilyl (TES) allyl ether **158e** and trimethylsilyl (TMS) allyl ether **155** provided notably improved yields (Table 3.1, entries 5–6). This is likely due to the increased accessibility of the nucleophilic oxygen resulting from reduced steric bulk of the appended silyl group. Lowering the equivalences of **155** from 2.0 to 1.5 lowered the yield (entry 7), but by increasing the amount of LiHMDS to 2.5 equivalents furnished **159** in 87% yield after only 2 hours of heating (entry 8). Decreasing the catalyst loading to 5 mol% resulted in lower yield (entry 9). The presence of both catalyst and LiHMDS was crucial for productive chemistry (entries 10 and 11).

Table 3.1. *Reaction optimization of Claisen cascade reaction.*



Entry	R	Ether	Catalyst	LiHMDS	Yield[a]
1	*Et (**158a**)*	*2.0 equiv*	*10 mol%*	*1.5 equiv*	*41%*
2	*allyl (**158b**)*	*2.0 equiv*	*10 mol%*	*1.5 equiv*	*58%*
3	*TIPS (**158c**)*	*2.0 equiv*	*10 mol%*	*1.5 equiv*	*0%*
4	*TBS (**158d**)*	*2.0 equiv*	*10 mol%*	*1.5 equiv*	*41%*
5	*TES (**158e**)*	*2.0 equiv*	*10 mol%*	*1.5 equiv*	*56%*
6	*TMS (**155**)*	*2.0 equiv*	*10 mol%*	*1.5 equiv*	*78%*
7	*TMS (**155**)*	*1.5 equiv*	*10 mol%*	*1.5 equiv*	*44%*
8	*TMS (**155**)*	*2.0 equiv*	*10 mol%*	*2.5 equiv*	*87%*
9	*TMS (**155**)*	*2.0 equiv*	*5 mol%*	*2.5 equiv*	*59%*
10	*TMS (**155**)*	*2.0 equiv*	*0 mol%*	*2.5 equiv*	*0%*
11	*TMS (**155**)*	*2.0 equiv*	*10 mol%*	*0 equiv*	*trace*

[a] *Yields determined by ^{1}H NMR using $MeNO_2$ as an internal standard.*

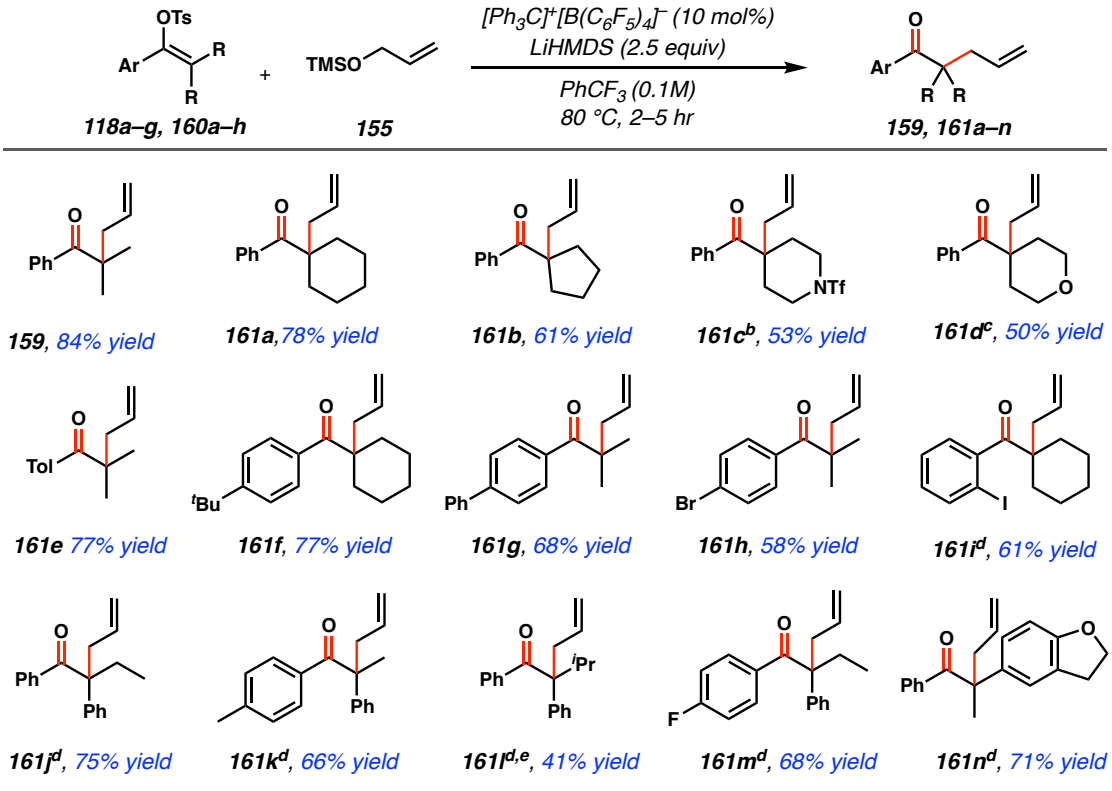
3.3 INVESTIGATION OF SCOPE FOR CLAISEN REARRANGEMENT

3.3.1 Scope of Vinyl Tosylates

To explore the generality of this reaction, a range of vinyl tosylates were prepared and subjected to the optimized reaction conditions. We were pleased to find that a range of sterically-congested products could be accessed in moderate-to-good yield (Scheme 3.5). First, ketone **159** was isolated on a 2.0 mmol scale in 84% yield. Cyclohexyl and cyclopentyl substituents on the vinyl tosylate (**118a** and **160a**) furnished products **161a** and **161b** in moderate yields. Lewis basic heterocyclic substrates containing piperidine (**160b**), tetrahydropyran (**160c**), and dihydrobenzofuran (**160h**) groups were compatible with these Lewis acidic conditions, delivering allylated products (**161c**, **161d**, and **161n**) in 50–71%

yield. Both electron-rich (**118c**, **118d,** and **160e**) and -deficient (**118f** and **160g**) vinyl tosylates led to the desired products in moderate-to-good yields. Notably, aryl bromides (**118f**) and iodides (**118g**), which can be labile under transition metal-catalyzed processes, were also well-tolerated. Diaryl vinyl tosylates could also undergo the tandem C–O coupling/Claisen rearrangement reaction to form products **161j–n** in good yields. However, through optimization it was found that better yields were obtained with diallyl ether **158b** instead of **155** with this substrate class. Variation of the alkyl substituents were demonstrated, wherein sterically-congested isopropyl product **161l** could be accessed with slightly diminished yield.

Scheme 3.5. *Scope of vinyl tosylates for Claisen rearrangement.*



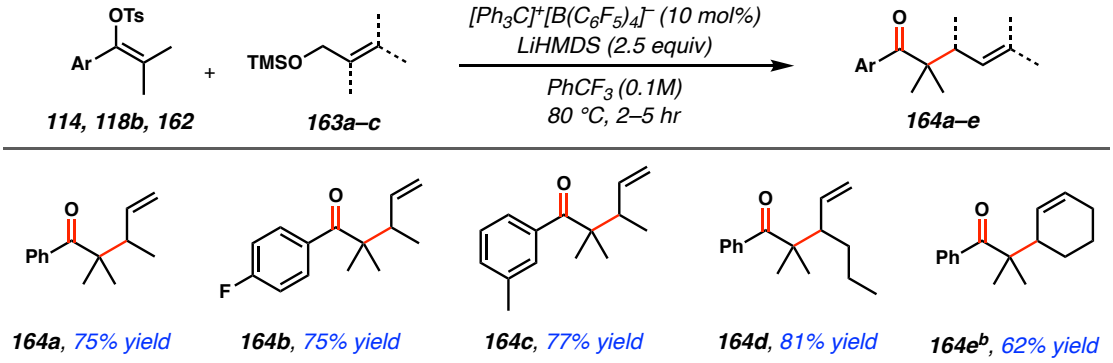
159, 84% yield | 161a,78% yield | 161b, 61% yield | 161c[b], 53% yield | 161d[c], 50% yield

[a]Isolated yield after column chromatography on 0.20 mmol scale with **155** (2 equiv) unless otherwise noted. [b]0.05 M, 20 mol% catalyst, 100 °C, 24 hr, 1.5 equiv LiHMDS. [c]0.05 M, 3 equiv LiHMDS. [d]Diallyl ether (**158b**) (2 equiv) used instead of TMS allyl ether (**155**). [e]95 °C.

3.3.2 Scope of TMS Allyl Ethers

After the vinyl tosylate coupling partner was explored, the allyl ether component (**163a–c**) was also surveyed (Scheme 3.6). By using terminally alkylated allyl ethers (**163a**, **163b**) branched products (**164a–d**) were selectively accessed in good yields, up to 81% yield. Using these mild conditions to access branched α-allylated ketone products offers an alternative approach to transition-metal catalyzed formation of branched ketone products.[53] Additionally, it was found that cyclohexene product **164e** could also be formed in 62% yield.

Scheme 3.6. *Scope of TMS allyl ether to access branched products.*

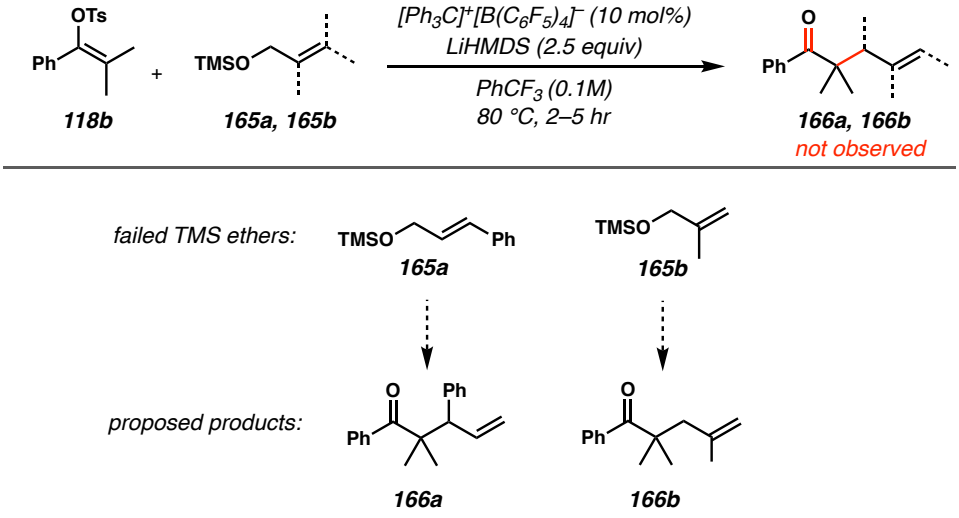


[a]Isolated yield after column chromatography on 0.20 mmol scale with TMS allyl ether (2 equiv) unless otherwise noted. [b]5 equiv.

Despite the initial success of surveying ethers to access branched α-allylated products, other ethers (**165a** and **165b**) did not prove as fruitful (Scheme 3.7). Although vinyl tosylate **118b** was consumed, no desired product was observed by crude NMR. Instead, oligomeric products are suspected to be the result, as indicated by broad peaks in the crude NMR spectra. With ether **165a**, <5% of the desired product could be determined by NMR. The failure of ether **165a** could be rationalized in two ways: the rearrangement

of the allyl vinyl ether intermediate could perhaps be too sterically challenged, or it is also possible that the phenyl could be directly reacting with the vinyl cation via Friedel–Crafts.[54,55] When testing vinyl ether **165b**, it was surprising that no product was observed. However, studies have been reported that methyl substituents at that position can decelerate the rearrangement.[3]

Scheme 3.7. *Unsuccessful TMS Ethers for Claisen cascade reaction.*



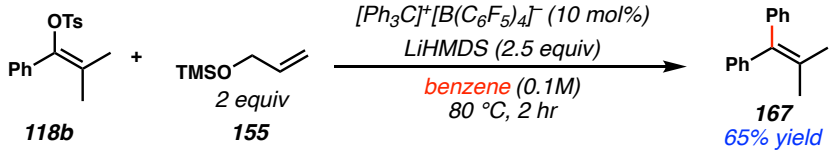
3.4 MECHANISTIC STUDIES

3.4.1 Support for Proposed Claisen Rearrangement

Following our substrate scope studies, we carried out experiments to probe the mechanism. Vinyl sulfonate ionization by Li-WCA salts has been previously demonstrated as an effective strategy to generate vinyl carbocations catalytically by our group.[52] Moreover, we observed in the present study that running the reaction in benzene solvent resulted in significant Friedel-Crafts reactivity to form **167**, which is a known reaction

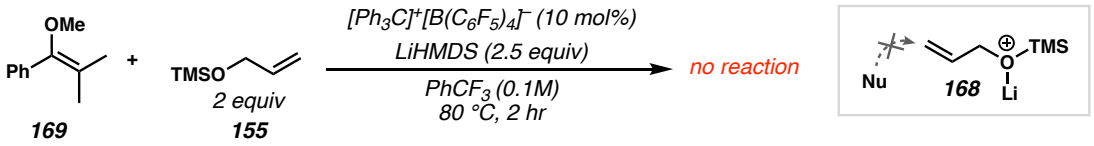
pathway of vinyl carbocations (Scheme 3.8).[54,55] We propose that in non-nucleophilic solvents such as trifluorotoluene, weakly nucleophilic silyl ethers are capable of trapping electrophilic vinyl cations.

Scheme 3.8. *Support for vinyl cation intermediacy.*



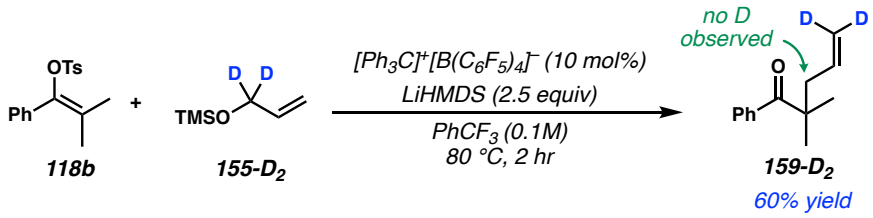
Since TMS allyl ether does have a Lewis basic oxygen center, an alternative reaction pathway could involve Lewis acid activation of the allyl ether to generate **168**, which can then undergo nucleophilic attack from the vinyl tosylate via a S_N2' mechanism (Scheme 3.9). To probe this hypothesis, methoxy vinyl ether **169** was prepared, as if this was the operative mechanism, this vinyl ether variant should also be competent under this reaction pathway. However, no reaction with **169** was observed under the optimized reaction conditions. This outcome thus supports the proposed intermediacy of a vinyl cation intermediate that gets trapped with TMS allyl ether.

Scheme 3.9. *Probing alternative reaction pathway via TMS allyl ether activation.*



The proposed Claisen rearrangement was also probed by performing the developed reaction with deuterated allyl TMS ether **155-D$_2$** (Scheme 3.10). **155-D$_2$** was prepared and subjected to the optimized reaction conditions, furnishing product **159-D$_2$** with no sign of deuterium incorporation at the allylic position by NMR. This result is consistent with a concerted [3,3] rearrangement. To note, the yield of **159-D$_2$** was moderately lower than the developed reaction with TMS allyl ether **155**. This is attributed to the fact that **155-D$_2$** had to be synthetically prepared, as opposed to commercially available **155**, and due to volatility of the ether, residual solvent and silicone grease remained in the ether sample. This ultimately seemed to impact the efficiency of the reaction, but nonetheless the product was obtained in moderate yield.

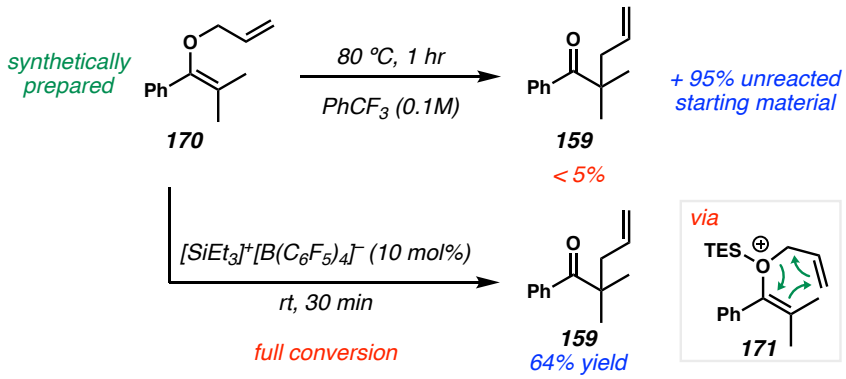
Scheme 3.10. *Claisen rearrangement with deuterated TMS allyl ether.*



We next wanted to address our hypothesis that an initial cationic vinyl silyloxonium intermediate was undergoing a charge-accelerated Claisen rearrangement (Scheme 3.11). While the reactions in this study are heated to 80 ºC, this temperature is required to achieve efficient ionization of the vinyl tosylate to generate a high energy vinyl carbocation; the proposed cationic [3,3] rearrangement could be facile at lower temperatures, especially if the rearrangement is accelerated by a charged intermediate. We therefore prepared allyl vinyl ether **170** and found that the neutral Claisen rearrangement is sluggish at 80 ºC (<5%

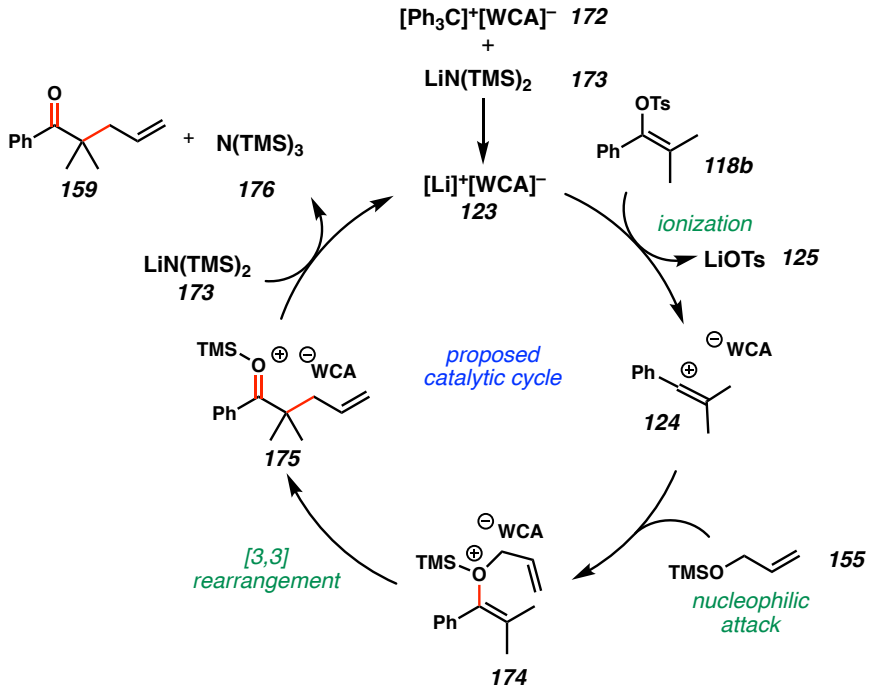
yield after 1 hour) in $PhCF_3$ solvent. However, it was found that the addition of catalytic $[SiEt_3]^+[B(C_6F_5)]^-$ resulted in rapid conversion to the Claisen product (**159**) at room temperature within 30 minutes (Scheme 3.11). The Lewis acidic silylium species likely coordinates to the Lewis basic oxygen center of the allyl vinyl ether, resulting in charged intermediate **171**. This is consistent with our proposal and reported accelerating effects of Claisen rearrangements induced by positive charge.[39,42,47–51]

Scheme 3.11. *Neutral vs cationic Claisen rearrangement of allyl vinyl ether.*



Based on the conducted mechanistic experiments, our proposed mechanism commences with *in-situ* generation of the Lewis acidic $[Li]^+[B(C_6F_5)_4]^-$, denoted as $[Li]^+[WCA]^-$ (Scheme 3.12).[52] Ionization of vinyl tosylate **118b** generates a vinyl carbocation (**124**)[56], which is trapped by the allyl ether nucleophile (**155**) to generate a silyloxonium (**174**) that is poised to undergo a cationic [3,3] sigmatropic rearrangement to **175**. Following the rearrangement, desilylation by LiHMDS generates $N(TMS)_3$ (**176**) (observed by GC-FID) and ketone product **159**, while also regenerating catalytic $[Li]^+[B(C_6F_5)_4]^-$.

Scheme 3.12. *Proposed mechanism of Claisen cascade reaction.*

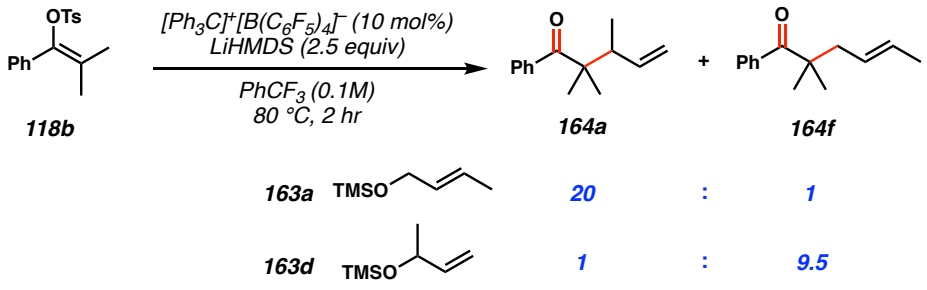


3.4.2 Product Distribution of Substituted Ethers

During our scope studies we found that ether **163a** gave low yields of a secondary product which was ultimately characterized as **164f** (20:1 ratio of **164a**/**164f**) (Scheme 3.13). Since deuterated allyl ether **155-D$_2$** demonstrated clean conversion to a single observable isotopomer, this result was unexpected and suggested a competing [1,3] rearrangement could be operative. Therefore, a constitutional isomer of the allyl ether (**163d**) was prepared and subjected to the reaction conditions, which furnished primarily the expected linear product (**164f**) arising from [3,3], but some amount of the branched product (**164a**) was also formed—this time, in an 9.5:1 ratio. In previously disclosed reactions by Rovis, Yamamoto, and Gansäuer, allyl vinyl ethers in the presence of strong

Lewis acids can lead to a mixture of products resulting from both [1,3] and [3,3] rearrangements.[57–59]

Scheme 3.13. *Product distribution of methyl substituted ethers.*



3.5 CONCLUDING REMARKS

In summary, we have disclosed a new catalytic C–O coupling/Claisen rearrangement cascade reaction using simple, commercially-available borate salts as catalysts. The reaction was demonstrated on various substrates, showcasing the ability to construct sterically-hindered C–C bonds. Notably, this reaction uses simple starting materials, such as vinyl tosylates that are readily accessed from ketones and silyl allyl ethers that are often commercially available or synthesized in a single step from commercial alcohols. Mechanistic experiments were conducted, and these experiments support a cationic [3,3] rearrangement of a silyloxonium intermediate produced upon trapping of a catalytically-generated vinyl cation by allyl ether. Additional mechanistic and computational studies are underway to further understand this rearrangement.

3.6 EXPERIMENTAL SECTION

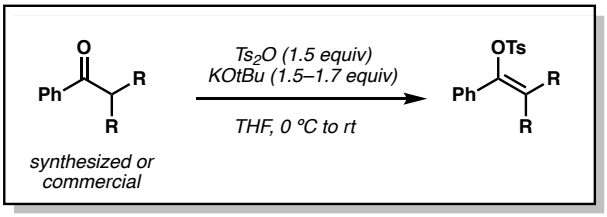
3.6.1 Materials and Methods

Unless otherwise stated, all reactions were performed in an MBraun or VAC glovebox under nitrogen atmosphere with ≤ 0.5 ppm O_2 levels. All glassware and stir-bars were dried in a 160 °C oven for at least 12 hours and cycled directly into the glovebox for use. Solid substrates were dried on high vacuum over P_2O_5 overnight, and liquid substrates were dried in a glovebox by passing through activated neutral alumina. All solvents were rigorously dried before use. Benzene and trifluorotoluene were degassed and dried in a JC Meyer solvent system and stored inside a glovebox. Cyclohexane was distilled over potassium. *o*-Difluorobenzene was distilled over CaH_2. All other solvents used for substrate synthesis were dried in a JC Meyer solvent system. Preparatory thin layer chromatography (TLC) was performed using Millipore silica gel 60 F_{254} pre-coated plates (0.25 mm) and visualized by UV fluorescence quenching. SiliaFlash P60 silica gel (230-400 mesh) was used for flash chromatography. NMR spectra were recorded on a Bruker 400 MHz with Prodigy cryoprobe (^1H, ^{13}C), a Bruker 400 MHz (^1H, ^{19}F), and a Varian 500 MHz (^1H). ^1H NMR spectra are reported relative to $CDCl_3$ (7.26 ppm) unless noted otherwise. Data for ^1H NMR spectra are as follows: chemical shift (ppm), multiplicity, coupling constant (Hz), integration. Multiplicities are as follows: s = singlet, d = doublet, t = triplet, dd = doublet of doublet, dt = doublet of triplet, ddd = doublet of doublet of doublet, td = triplet of doublet, m = multiplet. ^{13}C NMR spectra are reported relative to $CDCl_3$ (77.1 ppm) unless noted otherwise. IR Spectra were record on a Thermo Scientific Nicolet iS50 FT-IR and are reported in terms of frequency absorption (cm^{-1}). High resolution mass spectra (HR-MS) were recorded on an Agilent 6230 time-of-flight LC/MS

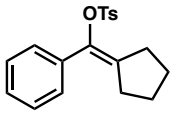
(LC/TOF) using electrospray ionization (ESI) or acquired by the Caltech Mass Spectral Facility by Field Ionization/Field Desorption mass spectrometry using a JEOL AccuTOF GC-Alpha (JMS-T2000GC) mass spectrometer interfaced with an Agilent 8890 GC system. Ions were detected as M+ (radical cations). All commercial chemicals and reagents were used as received, unless otherwise noted. Solid lithium hexamethyldisilazide and potassium hexamethyldisilazide were purchased from Sigma Aldrich and brought in the glovebox as received. Trityl tetrakis(pentafluorophenyl)borate was purchased from TCI and brought in the glovebox and used as received. Commercial allyloxytrimethylsilane (**155**) (Sigma Aldrich) and diallylether (**158b**) (TCI) were dried by passing through activated neutral alumina in a glovebox. TMSCl was distilled prior to use. Other reagents include: imidazole (Fisher Scientific), KO*t*Bu (Sigma Aldrich), iodomethane and iodoethane (Oakwood Chemicals), Ts_2O (Oakwood Chemicals), and DMEA (Oakwood Chemicals). Commercial alcohols were purchased from Sigma Aldrich, Oakwood Chemicals, and Fisher Scientific.

3.6.2 Preparation of Vinyl Tosylates

For the preparation of vinyl tosylates **114** and **118a–g**, see section **2.7.2** and **Appendix 1** for spectra data. Vinyl tosylates **160a–h** and **162** were prepared from ketones that were either commercially available or synthetically prepared according to the following procedure:



General Procedure 1: To a flame-dried flask, commercially available ketone or otherwise synthetically made (1.0 equiv), was dissolved in THF (0.33 M). The solution was cooled to 0 ºC, and then a solution of KOtBu (1.5–1.7 equiv, 1 M THF) was added dropwise. The resulting solution was then stirred at 0 ºC for 2 hours. Next, Ts_2O (1.5 equiv) was added as a solution in THF (0.6 M) to the enolate solution with vigorous stirring, and then the solution was allowed to warm to room temperature and stirred until completion. Once starting material is consumed, the reaction was diluted with EtOAC and water. The organic layer was separated, and the aqueous layer was extracted 3x, dried over Na_2SO_4, filter, concentrated *in vacuo*, and purified by silica flash column chromatography (ether/hexanes) to give vinyl tosylate.



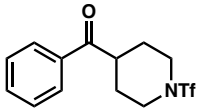
cyclopentylidene(phenyl)methyl 4-methylbenzenesulfonate (160a) was prepared according to *General Procedure 1* from commercially available ketone on a 15.0 mmol scale (2.6g, 53% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.49 (m, 2H), 7.20 – 7.07 (m, 7H), 2.54 (dtd, *J* = 7.4, 3.6, 1.4 Hz, 2H), 2.42 (qt, *J* = 5.6, 2.6 Hz, 2H), 2.35 (s, 3H), 1.68 (dqd, *J* = 5.5, 4.3, 2.0 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.4, 138.9, 138.4, 134.8, 134.4, 129.3, 128.1, 127.8, 127.8, 127.7, 127.6, 31.6, 31.0, 27.2, 25.7, 21.6.

FT-IR (neat film NaCl): 3056, 2956, 2869, 1598, 1494, 1445, 1366, 1292, 1259, 1189, 1175, 1095, 997, 951, 820, 805, 784, 697, 552 cm^{-1}.

HR-MS (FI^+) m/z: [M] Calculated for $C_{19}H_{20}O_3S$ 328.1133; Found 328.1139.



phenyl(1-((trifluoromethyl)sulfonyl)piperidin-4-yl)methanone (177)

To a flame dried flask, commercially available 4-Benzoylpiperidine hydrochloride (1.10 g, 1.0 equiv, 4.9 mmol) was added followed by dry DCM (16 mL). Dry triethylamine (3.4 mL, 5 equiv, 24.4 mmol) was added next and the reaction was cooled to 0 ºC. Anhydrous Tf_2O (900 uL, 1.1 equiv, 5.4 mmol) was then added and the reaction was allowed to warm to room temperature and stir overnight. The next day water was added and the organic layer was washed 3x with water and then dried over Na_2SO_4. The crude reaction mixture was purified via flash column chromatography 10 → 15% ethyl acetate/hexanes to afford **177** as a solid (600 mg, 38%).

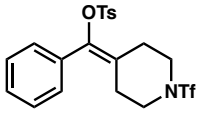
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 – 7.91 (m, 2H), 7.64 – 7.56 (m, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 3.99 (d, *J* = 13.2 Hz, 2H), 3.53 – 3.45 (m, 1H), 3.29 (s, 2H), 2.05 – 1.99 (m, 2H), 1.92 (dtd, *J* = 14.4, 10.6, 4.1 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.9, 135.4, 133.5, 128.9, 128.25, 120.1 (q, *J* = 323.1 Hz), 45.9, 28.1.

^{19}F NMR (376 MHz, $CDCl_3$) δ -74.2.

FT-IR (neat film NaCl): 2951, 2871, 1677, 1597, 1582, 1448, 1381, 1367, 1337, 1313, 1296, 1269, 1228, 1183, 1145, 1110, 1062, 950, 844, 784, 763, 703, 688, 667, 586, 578, 469 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{13}H_{15}F_3NO_3S^+$ 322.0720; Found 322.0734.



phenyl(1-((trifluoromethyl)sulfonyl)piperidin-4-ylidene)methyl 4-methylbenzenesulfonate (160b) was prepared according to *General Procedure 1* from **177** on a 1.8 mmol scale (500 mg, 56% yield).

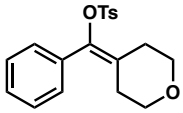
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.37 (m, 2H), 7.25 – 7.14 (m, 3H), 7.14 – 7.03 (m, 4H), 3.89 – 3.14 (broad m, 4H), 2.66 (broad, 2H), 2.42 (t, J = 5.8 Hz, 2H), 2.35 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8, 142.1, 133.8, 132.4, 129.6, 129.5, 128.9, 128.2, 128.0, 126.1, 120.1 (q, J = 323.2 Hz), 47.3, 47.1, 29.4, 28.3, 21.6.

^{19}F NMR (376 MHz, $CDCl_3$) δ -75.6.

FT-IR (neat film NaCl): 3059, 2926, 2878, 1598, 1388, 1370, 1226, 1187, 1175, 1150, 1095, 1017, 947, 867, 785, 701, 676, 590, 553 cm^{-1}.

HR-MS (ESI) m/z: [M+Na]+ Calculated for $C_{20}H_{20}F_3NNaO_5S_2$ 498.0627; Found 498.0626.



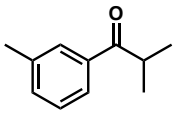
phenyl(tetrahydro-4*H*-pyran-4-ylidene)methyl 4-methylbenzenesulfonate (160c) was prepared according to *General Procedure 1* from commercially available ketone on a 15.8 mmol scale (3.5, 64% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.39 (m, 2H), 7.15 (dddd, J = 12.3, 7.9, 6.5, 3.3 Hz, 5H), 7.11 – 7.04 (m, 2H), 3.72 (t, J = 5.5 Hz, 2H), 3.67 – 3.59 (m, 2H), 2.53 (dd, J = 5.9, 5.1 Hz, 2H), 2.34 (s, 3H), 2.32 (m, 2H).

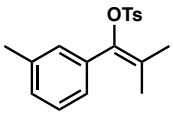
^{13}C NMR (101 MHz, $CDCl_3$) δ 144.5, 140.2, 134.1, 133.1, 129.6, 129.3, 128.6, 128.4, 128.1, 128.0, 68.3, 68.2, 30.5, 29.3, 21.6.

FT-IR (neat film NaCl): 3057, 2962, 2910, 2847, 1598, 1493, 1366, 1295, 1188, 1174, 1094, 1014, 988, 785, 699, 574, 557 cm^{-1}.

HR-MS (ESI) m/z: [M+Na]+ Calculated for $C_{19}H_{20}NaO_4S$ 367.0975; Found 367.0982.



2-methyl-1-(*m*-tolyl)propan-1-one (178) was prepared according to literature procedure[60] and matched the NMR data in the literature.[61]



2-methyl-1-(*m*-tolyl)prop-1-en-1-yl 4-methylbenzenesulfonate (162) was prepared according to *General Procedure 1* from **178** on a 15.4 mmol scale (0.546 g, 11% yield).

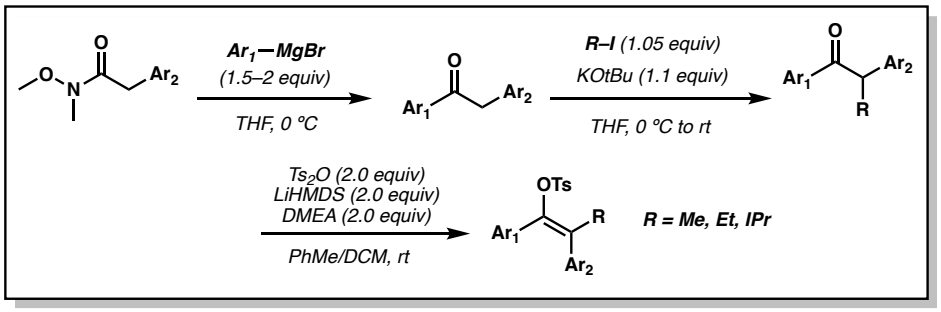
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.38 (m, 2H), 7.07 – 7.01 (m, 3H), 7.00 – 6.91 (m, 2H), 6.84 (tt, J = 1.7, 0.8 Hz, 1H), 2.34 (s, 3H), 2.15 (s, 3H), 1.90 (s, 3H), 1.75 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1, 141.5, 137.3, 134.5, 133.6, 130.1, 129.1, 128.6, 128.0, 127.6, 126.9, 126.2, 21.6, 21.2, 20.1, 19.1.

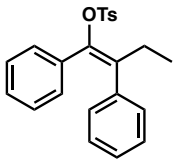
FT-IR (neat film NaCl): 2993, 2918, 2860, 1599, 1450, 1364, 1189, 1175, 1083, 1019, 911, 822, 805, 791, 714, 674, 587, 569, 549 cm^{-1}.

HR-MS (ESI) m/z: [M+Na]+ Calculated for $C_{18}H_{20}NaO_3S$ 339.1025; Found 339.1027.

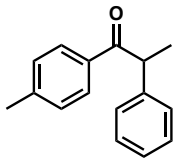
Vinyl tosylates **160d–h** were prepared according to the following reaction scheme:



General Procedure 2: Diaryl vinyl tosylate substrates were synthesized according to published literature procedures from the corresponding Weinreb amide[62,63] or commercially available ketones. The tosylation step follows a known literature procedure for diaryl vinyl tosylate substrates.[64,65]



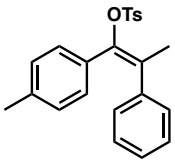
(*E*)-1,2-diphenylbut-1-en-1-yl 4-methylbenzenesulfonate (160d) was prepared according to known literature procedures from commercially available 1,2-diphenylbutan-1-one and spectra matched the reported literature.[64]



2-phenyl-1-(*p*-tolyl)propan-1-one (179)

To a flame dried flask, commercially available 2-phenyl-1-(*p*-tolyl)ethan-1-one (1.17 g, 1 equiv, 5.54 mmol) was added followed by THF (11 mL) and cooled to 0 °C. Then, a

solution of KOtBu (747 mg, 1.2 equiv, 6.65 mmol) in THF (7 ml) was added dropwise. The reaction was allowed to stir for 20 minutes, and then iodomethane (0.38 mL, 1.1 equiv, 6.1 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred until starting material was consumed as determined by TLC (5% diethyl ether/hexanes). Then, 2M HCl was added and the reaction was extracted EtOAc 3x. The combined organics were washed with water, brine, and then dried of MgSO4. The crude mixture was purified via flash column chromatography 3% diethyl ether/pentanes to afford an oil **179** (0.852 g, 73% yield), which matched the NMR data in the literature.[66]



(*E*)-2-phenyl-1-(p**-tolyl)prop-1-en-1-yl 4-methylbenzenesulfonate (160e)** was prepared according to known literature procedure for similar vinyl tosylates[64]: to a flame dried Schlenk flask was added LiHMDS (1.27 g, 2 equiv, 7.6 mmol) inside of a glovebox. The Schlenk flask was removed and anhydrous PhMe (8.4 mL) was added followed by DMEA (0.82 mL, 2 equiv, 7.6 mmol). To another flame dried flask was added **179** (0.852 g, 1 equiv, 3.8 mmol) followed by anhydrous PhMe (3.8 mL). The ketone solution was then added dropwise to the LiHMDS solution at room temperature. The reaction was allowed to stir for 20 minutes. To another flame dried flask was added Ts_2O (2.48 g, 2 equiv, 7.6 mmol) with anhydrous DCM (20 mL). The Ts_2O solution was then added dropwise to the enolate solution with vigorous stirring. *Note: the solution becomes very thick.* The reaction was monitored by TLC (20% diethyl ether/hexanes), and after 1 hour it was complete. A few mLs of 1M NaOH was then added, and the solution became homogenous. Additional

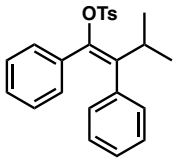
water was added, and then reaction was extracted 3x with diethyl ether. The combined organics were then dried over Na_2SO_4 and the crude mixture was concentrated *in vacuo*. The material was purified by flash column chromatography (5% diethyl ether/hexanes) to afford pure **160e** as a white solid (600 mg, 43% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.47 (m, 2H), 7.20 – 7.14 (m, 3H), 7.13 – 7.09 (m, 2H), 7.07 – 7.01 (m, 2H), 6.80 (d, J = 8.2 Hz, 2H), 6.75 – 6.69 (m, 2H), 2.37 (s, 3H), 2.18 (s, 3H), 2.17 (s, 3H).

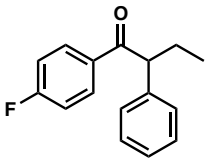
^{13}C NMR (101 MHz, $CDCl_3$) δ 144.4, 143.6, 140.2, 137.7, 134.5, 131.1, 130.2, 129.8, 129.3, 128.8, 128.2, 128.1, 127.1, 21.7, 21.3, 19.9.

FT-IR (neat film NaCl): 3054, 3028, 2921, 2861, 1598, 1442, 1367, 1190, 1176, 1085, 1040, 967, 854, 823, 814, 768, 760, 700, 670, 581, 558, 545 cm^{-1}.

HR-MS (ESI) m/z: [M+Na]+ Calculated for $C_{23}H_{22}NaO_3S$ 401.1182; Found 401.1184.



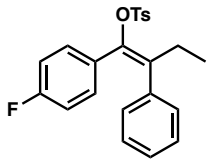
(*E*)-3-methyl-1,2-diphenylbut-1-en-1-yl 4-methylbenzenesulfonate (160f) was prepared according to literature procedure and matched the NMR data in the literature.[64]



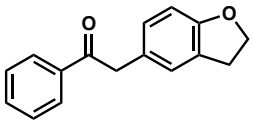
1-(4-fluorophenyl)-2-phenylbutan-1-one (180)

To a flame dried flask, commercially available 1-(4-fluorophenyl)-2-phenylethan-1-one

(750 mg, 1 equiv, 3.50 mmol) was added followed by THF (7 mL) and cooled to 0 ºC. Then, a solution of KOtBu (471 mg, 1.2 equiv, 4.20 mmol) in THF (3.8 ml) was added dropwise. The reaction was allowed to stir for 20 minutes, and then iodoethane (0.37 mL, 1.3 equiv, 4.55 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred until starting material was consumed as determined by TLC (5% diethyl ether/hexanes). Then, 2M HCl was added and the reaction was extracted EtOAc 3x. The combined organics were washed with water, brine, and then dried of MgSO4. The crude mixture was purified via flash column chromatography 3% diethyl ether/pentanes to afford an oil **180** (780 mg, 92% yield), which matched the NMR data in the literature.[65]



(*E*)-1-(4-fluorophenyl)-2-phenylbut-1-en-1-yl 4-methylbenzenesulfonate (160g) was prepared according to known literature procedures from **180**. Spectra matched the reported literature.[65]



2-(2,3-dihydrobenzofuran-5-yl)-1-phenylethan-1-one (**181**) was prepared according to a known literature procedure from commercially available 2,3-dihydrobenzofuran-5-acetic acid.[67]

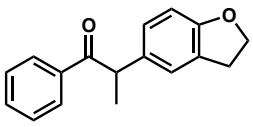
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 7.96 (m, 2H), 7.61 – 7.51 (m, 1H), 7.46 (ddt, *J* = 8.3,

6.7, 1.2 Hz, 2H), 7.10 (d, *J* = 1.9 Hz, 1H), 6.99 (ddt, *J* = 8.2, 2.0, 0.8 Hz, 1H), 6.74 (d, *J* = 8.1 Hz, 1H), 4.54 (t, *J* = 8.7 Hz, 2H), 4.21 (s, 2H), 3.18 (t, *J* = 8.7 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.2, 159.2, 136.7, 133.2, 129.2, 128.7, 128.7, 127.6, 126.3, 126.1, 109.4, 71.4, 44.9, 29.8.

FT-IR (neat film NaCl): 3057, 2961, 2894, 1675, 1615, 1596, 1579, 1489, 1447, 1321, 1275, 1241, 1197, 1103, 982, 941, 926, 804, 750, 689, 591, 518 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{16}H_{15}O_2$ 239.1067; Found 237.1070.



2-(2,3-dihydrobenzofuran-5-yl)-1-phenylpropan-1-one (182)

To a flame dried flask was added **181** (600 mg, 1 equiv, 2.52 mmol) followed by THF (5 mL) and cooled to 0 ºC. Then, a solution of KOtBu (367 mg, 1.3 equiv, 3.27 mmol) in THF (3 ml) was added dropwise. The reaction was allowed to stir for 20 minutes, and then iodomethane (0.2 mL, 1.3 equiv, 3.27 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred until starting material was consumed as determined by TLC (15% diethyl ether/hexanes). Then, 2M HCl was added and the reaction was extracted EtOAc 3x. The combined organics were washed with water, brine, and then dried of MgSO4. The crude mixture was purified via flash column chromatography 3% diethyl ether/pentanes to afford white solid **182** (0.380 g, 60% yield.

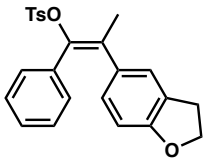
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.92 (m, 2H), 7.50 – 7.44 (m, 1H), 7.42 – 7.34 (m, 2H), 7.10 (t, *J* = 1.5 Hz, 1H), 7.03 (ddd, *J* = 8.2, 2.0, 1.0 Hz, 1H), 6.70 (d, *J* = 8.2 Hz, 1H), 4.63 (q, *J* = 6.8 Hz, 1H), 4.51 (td, *J* = 8.7, 1.2 Hz, 2H), 3.14 (td, *J* = 8.6, 3.0 Hz, 2H), 1.50

(d, J = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.7, 159.2, 136.6, 133.5, 132.8, 128.8, 128.5, 127.9, 127.7, 124.2, 109.6, 71.4, 47.3, 29.8, 19.8.

FT-IR (neat film NaCl): 3059, 2972, 2929, 2895, 1679, 1596, 1490, 1448, 1371, 1341, 1234, 1107, 1002, 982, 957, 944, 811, 739, 693 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{17}H_{17}O_2$ 253.1223; Found 253.1214.



(*E*)-2-(2,3-dihydrobenzofuran-5-yl)-1-phenylprop-1-en-1-yl 4-methylbenzenesulfonate (160h) was prepared according to known literature procedure[64,65] for similar vinyl tosylates from **182**: to a flame dried Schlenk flask was added LiHMDS (2.8 g, 2 equiv, 16.6 mmol) inside of a glovebox. The Schlenk flask was removed and anhydrous PhMe (18.5 mL) was added followed by DMEA (2.1 mL, 2 equiv, 16.6 mmol). To another flame dried flask was added **182** (2.1 g, 1 equiv, 8.3 mmol) followed by anhydrous PhMe (8.3 mL). The ketone solution was then added dropwise to the LiHMDS solution at room temperature. The reaction was allowed to stir for 20 minutes. To another flame dried flask was added Ts_2O (5.4 g, 2 equiv, 16.6 mmol) with anhydrous DCM (42 mL). The Ts_2O solution was then added dropwise to the enolate solution with vigorous stirring. *Note: the solution becomes very thick.* The reaction was monitored by TLC (20% diethyl ether/hexanes), and after 1 hour it was complete. A few mLs of 1M NaOH was then added, and the solution became homogenous. Additional water was added, and then reaction was extracted 3x with diethyl ether. The combined organics were then

dried over Na_2SO_4 and the crude mixture was concentrated *in vacuo*. The material was purified by flash column chromatography (15% diethyl ether/hexanes) to afford pure **160h** as a white solid (2.0 g, 59% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.43 (m, 2H), 7.11 – 7.06 (m, 2H), 7.04 – 6.97 (m, 1H), 6.95 – 6.90 (m, 4H), 6.89 (q, *J* = 1.3 Hz, 1H), 6.75 (ddd, *J* = 8.3, 1.9, 0.9 Hz, 1H), 6.55 (d, *J* = 8.2 Hz, 1H), 4.51 (t, *J* = 8.7 Hz, 2H), 3.06 (t, *J* = 8.7 Hz, 2H), 2.35 (s, 3H), 2.18 (s, 3H).

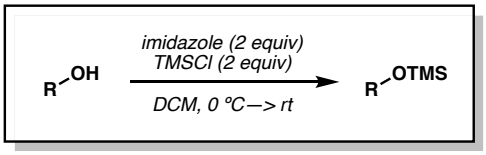
^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 144.4, 142.8, 134.5, 134.3, 132.1, 130.9, 129.9, 129.3, 128.9, 128.1, 127.5, 127.0, 125.4, 109.0, 71.4, 29.6, 21.6, 20.2.

FT-IR (neat film NaCl): 3055, 2919, 2858, 1609, 1598, 1490, 1444, 1366, 1236, 1189, 1176, 1038, 972, 943, 834, 773, 698, 676, 559 cm^{-1}.

HR-MS (ESI) m/z: [M+K]+ Calculated for $C_{24}H_{26}NO_4S$ 424.1577; Found 424.1577.

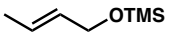
3.6.3 Preparation of Silyl Ethers

Silyl ethers **163a–c** and **165b** were prepared according to reported procedure.[68]



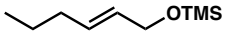
General Procedure 3: To a flame-dried flask was added solid imidazole (2 equiv) followed by dry DCM solvent to achieve 3 M concentration relative to imidazole. While under N_2 atmosphere, alcohol was added neat (1 equiv) then cooled to 0 ºC. Freshly distilled TMS–Cl (2 equiv) was added slowly dropwise while at 0 ºC, and the stirring mixture was allowed to warm to room temperature slowly overnight. The next morning, the reaction was

quenched with water, then the DCM layer was separated out. The aqueous layer was washed once more with pentane, and the combined organics were washed with brine then plugged through a short pad of silica gel. The filtrate was concentrated cold (0 ºC) and purified by either distillation or silica flash column chromatography as specified below. All pure silyl ethers were cycled into a nitrogen-filled glovebox and dried further by passing the neat material through activated neutral alumina.



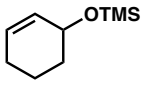
(*E*)-(but-2-en-1-yloxy)trimethylsilane (163a)

Prepared according to above *General Procedure 3* on 3.8 g (53.00 mmol) scale of starting commercially-available alcohol. The product was purified via silica gel flash chromatography (2% diethyl ether in pentane, visualized by $KMnO_4$ stain) and concentrated at 0 ºC to obtain pure silyl ether **163a** as a colorless oil, 4.8 g (53 % yield). Spectra matched reported literature.[69]



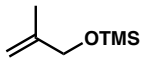
(*E*)-(hex-2-en-1-yloxy)trimethylsilane (163b)

Prepared according to above *General Procedure 3* on 2.00 g (20.00 mmol) scale of starting commercially-available alcohol. The product was purified via silica gel flash chromatography (2% diethyl ether in pentane, visualized by $KMnO_4$ stain) and concentrated at 0 ºC to obtain pure silyl ether **163b** as a colorless oil, 2.50 g (72% yield). Spectra matched reported literature.[69]



(cyclohex-2-en-1-yloxy)trimethylsilane (163c)

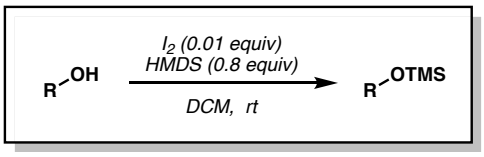
Prepared according to above *General Procedure 3* on 1.00 g (10.20 mmol) scale of starting commercially-available alcohol. The product was purified via silica gel flash chromatography (2% diethyl ether in pentane, visualized by $KMnO_4$ stain) and concentrated at 0 ºC to obtain pure silyl ether as a colorless oil, 1.40 g (81 % yield). Spectra matched reported literature.[70]



trimethyl((2-methylallyl)oxy)silane (165b)

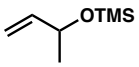
Prepared according to *General Procedure 3* on 59.4 mmol scale. The product was purified by flash column chromatography (3% diethyl ether/pentanes, visualized by $KMnO_4$ stain) to afford an oil (4 g, 47% yield). Spectra matched reported literature.[71]

Silyl ethers **163d** and **165a** were prepared according to a reported procedure[72]:



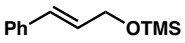
General Procedure 4: To a flame dried flask was added commercially available alcohol in anhydrous DCM to achieve 0.018 M. Iodine was then added (0.01 equiv). Distilled HMDS (0.8 equiv) was then added dropwise. The reaction was monitored by TLC (visualization by $KMnO_4$ stain) and starting material was consumed after 30 minutes. Na_2S_2O3 (about 4g/1 mmol of alcohol) was added to the reaction and stirred for an additional 30 minutes.

The solution was then filtered through a pad of silica gel and washed with DCM. The solution was concentrated at 0 ºC and purified by flash column chromatography (3% diethyl ether/pentanes) to afford an oil.



(but-3-en-2-yloxy)trimethylsilane (163d)

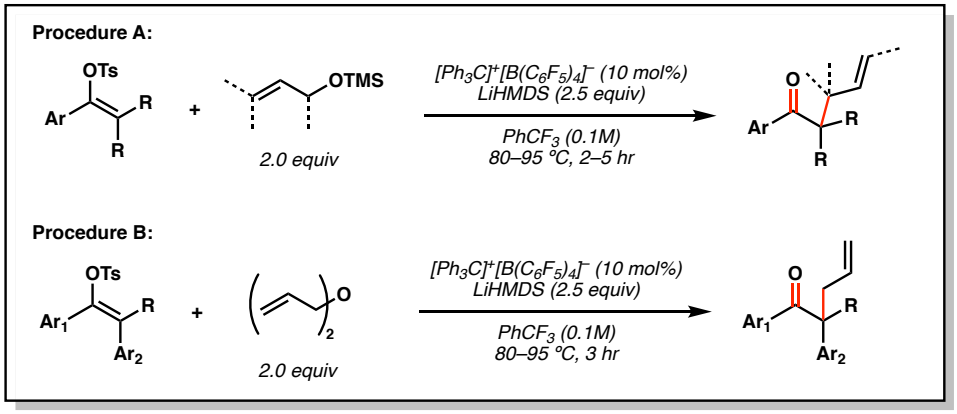
Prepared according to *General Procedure 4* on 24.4 mmol scale. The product was purified by flash column chromatography (3% diethyl ether/pentanes, visualized by $KMnO_4$ stain) to afford an oil (1.5 g, 43% yield). Spectra matched reported literature.[73]



(cinnamyloxy)trimethylsilane (165a)

Prepared according to *General Procedure 4* on 11.0 mmol scale. The product was purified by flash column chromatography (3% diethyl ether/pentanes) to afford a yellow solid (2.0 g, 90% yield). Spectra matched reported literature.[72]

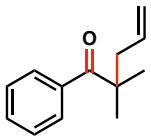
3.6.4 Catalytic Claisen Cascade Coupling Reaction



General Procedure A: All catalytic Claisen cascade coupling reactions were conducted in a well-maintained glove box (O_2, H_2O <0.5 ppm) on 0.2 mmol scale (of vinyl tosylate substrate). To a dram vial equipped with a magnetic stir bar was added $[Ph_3C]^+[B(C_6F_5)_4]^-$ catalyst (10 mol%), followed by LiHMDS (2.5 equivalents), followed by $PhCF_3$ solvent (2 mL). To this mixture was then added neat silyl allyl ether (2.0 equivalents) followed by solid vinyl tosylate (1 equivalent). The reaction was then sealed with a Teflon cap and heated for 2–5 hours depending on the substrate (reaction temperature were typically 80 ºC, but for a few substrates higher reaction temperatures were required as indicated below). The reactions were monitored by TLC, typically using 10% ethyl acetate in hexanes for the mobile phase. Once the reaction was completed, the vial was removed from the glovebox. The reaction was diluted with diethyl ether and plugged through silica gel (pushing through with diethyl ether) and concentrated *in vacuo*. The crude material was purified by flash column chromatography, (typically 2–10% diethyl ether/hexanes, depending on the product polarity) then dried on high vacuum to obtain material that is pure by 1 H NMR.

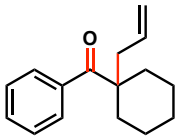
General Procedure B: A slightly modified procedure was followed when substrates

contained an additional aryl group in the α-position. While Procedure A still worked for this substrate class, it was found through optimization that diallyl ethers provided improved yields over silyl ally ethers. Therefore, the only modification for General Procedure B as compared to General Procedure A is that diallyl ether is used instead of TMS allyl ether, according to the graphic above.



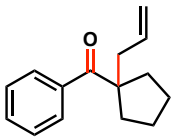
2,2-dimethyl-1-phenylpent-4-en-1-one (159)

Following the *General Procedure A* with **118b**. The reaction was complete after 2 hr. The product was purified by silica gel flash column chromatography (2% diethyl ether/hexanes) to obtain 31.7 mg of a pale yellow oil (84% yield). The spectra matched reported literature.[74]



(1-allylcyclohexyl)(phenyl)methanone (161a)

Following the *General Procedure A* with **118a**. The reaction was complete after 2 hr. The product was purified by silica gel flash column chromatography (3% diethyl ether/hexanes) to obtain 35.4 mg of a pale yellow oil (78% yield). The spectra matched reported literature.[75]



(1-allylcyclopentyl)(phenyl)methanone (161b)

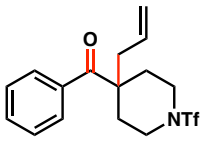
Following the *General Procedure A* with **160a**. The reaction was complete after 2 hr. The product was purified by silica gel flash column chromatography (3% diethyl ether/hexanes) to obtain 26.0 mg of a pale yellow oil (61% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.82 (m, 2H), 7.52 – 7.46 (m, 1H), 7.45 – 7.37 (m, 2H), 5.59 (ddt, *J* = 17.3, 10.1, 7.2 Hz, 1H), 4.96 – 4.82 (m, 2H), 2.60 (dt, *J* = 7.2, 1.3 Hz, 2H), 2.32 (dddd, *J* = 14.5, 7.5, 4.0, 1.5 Hz, 2H), 1.78 (dddd, *J* = 13.0, 7.2, 3.6, 1.2 Hz, 2H), 1.72 – 1.61 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 205.7, 137.2, 134.4, 131.8, 128.9, 128.3, 117.8, 58.9, 44.4, 35.9, 25.7.

FT-IR (neat film NaCl): 3074, 2953, 2868, 1672, 1597, 1578, 1446, 1275, 1216, 1179, 1009, 918, 716, 693, 430 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{15}H_{19}O$ 215.1430; Found 215.1428.



(4-allyl-1-((trifluoromethyl)sulfonyl)piperidin-4-yl)(phenyl)methanone (161c)

Following the *General Procedure A* with **160b** with slight modification. Reaction was ran at 0.05M with 20 mol% $[Ph_3C]^+[B(C_6F_5)_4]^-$ and 1.5 equiv of LiHMDS at 100 ºC for 24 hr. The product was purified by silica gel flash column chromatography (10% diethyl

ether/hexanes then 40% DCM/hexanes) to obtain 38.0 mg of clear oil (53% yield).

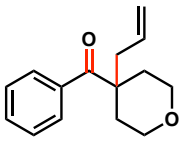
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.69 (m, 2H), 7.57 – 7.51 (m, 1H), 7.48 – 7.42 (m, 2H), 5.65 (ddt, *J* = 16.8, 10.2, 7.4 Hz, 1H), 5.15 – 5.06 (m, 2H), 3.74 (dd, *J* = 12.9, 4.4 Hz, 2H), 3.09 (broad singlet, 2H), 2.66 (dt, *J* = 7.4, 1.2 Hz, 2H), 2.49 (d, *J* = 14.0 Hz, 2H), 1.71 (ddd, *J* = 14.1, 11.5, 4.2 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 205.3, 138.1, 132.1, 131.5, 128.8, 127.9, 120.2 (q, *J* = 323.1 Hz), 119.6, 50.3, 44.2, 33.8.

^{19}F NMR (282 MHz, $CDCl_3$) δ -75.63.

FT-IR (neat film NaCl): 3078, 2977, 2927, 2886, 1672, 1597, 1449, 1387, 1342, 1226, 1184, 1135, 1053, 1004, 945, 765, 705, 591, 495 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{16}H_{19}F_3NO_3S$ 362.1032; Found 362.1031.



(4-allyltetrahydro-2*H*-pyran-4-yl)(phenyl)methanone (161d)

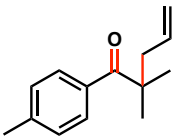
Following the *General Procedure A* with **160c** with slight modification. Reaction was ran at 0.05M with 3.0 equiv of LiHMDS. The reaction was complete after 12 hr. The product was purified by silica gel flash column chromatography (15% diethyl ether/hexanes) to obtain 22.3 mg of a pale yellow oil (50% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.66 (m, 2H), 7.52 – 7.46 (m, 1H), 7.45 – 7.39 (m, 2H), 5.69 (ddt, *J* = 16.8, 10.2, 7.4 Hz, 1H), 5.11 – 5.03 (m, 2H), 3.77 (dt, *J* = 11.9, 4.2 Hz, 2H), 3.44 (ddd, *J* = 11.9, 10.1, 2.6 Hz, 2H), 2.65 (dt, *J* = 7.4, 1.2 Hz, 2H), 2.33 – 2.27 (m, 2H), 1.71 (ddd, *J* = 14.1, 10.2, 4.1 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 206.9, 139.0, 132.5, 131.4, 128.5, 127.8, 118.9, 65.1, 50.2, 43.6, 34.5.

FT-IR (neat film NaCl): 3075, 2957, 2922, 2850, 1672, 1447, 1299, 1218, 1107, 1032, 976, 919, 793, 733, 699, 553 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{15}H_{19}O_2$ 231.1380; Found 231.1375.



2,2-dimethyl-1-(*p*-tolyl)pent-4-en-1-one (161e)

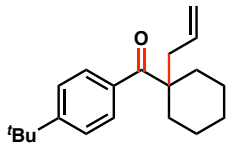
Following the *General Procedure A* with **118c**. The reaction was complete after 2 hr. The product was purified by silica gel flash column chromatography (3% diethyl ether/hexanes) to obtain 31.2 mg of a pale yellow oil (77% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.57 (m, 2H), 7.24 – 7.16 (m, 2H), 5.71 (ddt, *J* = 16.7, 10.2, 7.3 Hz, 1H), 5.06 – 4.96 (m, 2H), 2.50 (dt, *J* = 7.3, 1.2 Hz, 2H), 2.38 (s, 3H), 1.32 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 207.9, 141.6, 136.1, 134.3, 128.9, 128.3, 118.2, 47.7, 45.3, 26.0, 21.6.

FT-IR (neat film NaCl): 3076, 2977, 2927, 2873, 1671, 1640, 1608, 1468, 1386, 1251, 1171, 963, 917, 827, 755, 564 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{14}H_{19}O$ 203.1430; Found 203.1428.



(1-allylcyclohexyl)(4-(*tert*-butyl)phenyl)methanone (161f)

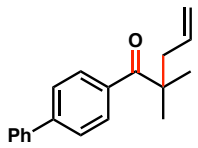
Following the *General Procedure A* with **118d**. The reaction was complete after 2 hr. The product was purified by silica gel flash column chromatography (3% diethyl ether/hexanes) to obtain 44.0 mg of a pale yellow oil (77% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.60 (m, 2H), 7.42 – 7.36 (m, 2H), 5.70 (ddt, *J* = 15.9, 11.0, 7.4 Hz, 1H), 5.05 – 4.98 (m, 2H), 2.56 (dt, *J* = 7.4, 1.3 Hz, 2H), 2.26 – 2.18 (m, 2H), 1.58 – 1.35 (m, 6H), 1.33 (s, 9H), 1.31 – 1.25 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.3, 154.2, 137.1, 133.7, 127.7, 125.1, 117.9, 52.5, 43.6, 34.9, 34.5, 31.3, 26.1, 23.0.

FT-IR (neat film NaCl): 3076, 2960, 2931, 2865, 1668, 1639, 1605, 1452, 1364, 1269, 1222, 1192, 1109, 995, 913, 844, 834, 716 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{21}H_{31}O$ 285.2213; Found 285.2212.



1-([1,1'-biphenyl]-4-yl)-2,2-dimethylpent-4-en-1-one (161g)

Following the *General Procedure A* with **118e**. The reaction was complete after 2 hr. The product was purified by silica gel flash column chromatography (3% diethyl ether/hexanes) to obtain 39.2 mg of a white solid (74% yield).

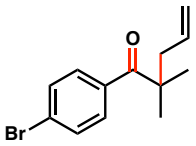
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.77 (m, 2H), 7.64 – 7.60 (m, 4H), 7.49 – 7.44 (m,

2H), 7.42 – 7.36 (m, 1H), 5.75 (ddt, J = 16.8, 10.3, 7.3 Hz, 1H), 5.08 – 5.00 (m, 2H), 2.53 (dt, J = 7.4, 1.2 Hz, 2H), 1.37 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.1, 143.8, 140.2, 137.6, 134.3, 129.1, 128.7, 128.1, 127.3, 126.9, 118.3, 47.8, 45.2, 26.0.

FT-IR (neat film NaCl): 3076, 3031, 2977, 2931, 1670, 1604, 1487, 1468, 1387, 1251, 1222, 1173, 965, 918, 850, 749, 679, 415 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{19}H_{21}O$ 265.1587; Found 265.1588.



1-(4-bromophenyl)-2,2-dimethylpent-4-en-1-one (161h)

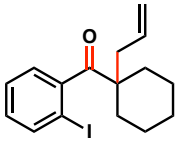
Following the *General Procedure A* with **118f**. The reaction was complete after 6 hr. The product was purified by silica gel flash column chromatography (3% diethyl ether/hexanes) to obtain 31.2 mg of a pale yellow oil (58% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 4H), 5.69 (ddt, J = 16.9, 10.2, 7.3 Hz, 1H), 5.06 – 4.97 (m, 2H), 2.47 (dt, J = 7.3, 1.2 Hz, 2H), 1.31 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 207.7, 137.8, 134.0, 131.6, 129.7, 125.9, 118.6, 47.9, 45.2, 25.9.

FT-IR (neat film NaCl): 3076, 2977, 2931, 2873, 1675, 1584, 1483, 1468, 1393, 1249, 1073, 1010, 919, 836, 758 cm^{-1}.

HR-MS (FD^+) m/z: [M] Calculated for $C_{13}H_{15}BrO$ 266.0306; Found 266.0219.



(1-allylcyclohexyl)(2-iodophenyl)methanone (161i)

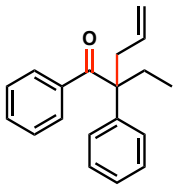
Following the *General Procedure B* with **118g**. The reaction was complete after 2 hr. The product was purified by silica gel flash column chromatography (3% diethyl ether/hexanes) to obtain 43.4 mg of a colorless oil (61% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.34 (td, *J* = 7.5, 1.2 Hz, 1H), 7.22 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.06 (ddd, *J* = 8.0, 7.3, 1.7 Hz, 1H), 5.84 (ddt, *J* = 16.0, 11.3, 7.4 Hz, 1H), 5.14 – 5.07 (m, 2H), 2.57 (dt, *J* = 7.3, 1.2 Hz, 2H), 1.91 (ddd, *J* = 13.2, 9.0, 4.0 Hz, 2H), 1.67 – 1.60 (m, 2H), 1.56 – 1.46 (m, 5H), 1.38 – 1.29 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 210.9, 145.5, 140.6, 134.2, 130.4, 127.2, 125.9, 118.1, 92.6, 52.2, 39.8, 33.2, 25.6, 22.1.

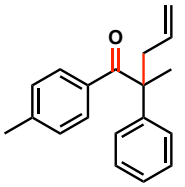
FT-IR (neat film NaCl): 3073, 2929, 2856, 1688, 1638, 1581, 1453, 1425, 1278, 1218, 1016, 996, 913, 765, 744, 653, 632 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{16}H_{20}IO$ 355.0553; Found 355.0553.



2-ethyl-1,2-diphenylpent-4-en-1-one (161j)

Following the *General Procedure B* with **160d**. The reaction was complete after 3 hr. The product was purified by silica gel flash column chromatography (3% diethyl ether/hexanes) to obtain 39.6 mg of a pale yellow oil (75% yield). Spectra match reported literature.[76]



2-methyl-2-phenyl-1-(*p*-tolyl)pent-4-en-1-one (161k)

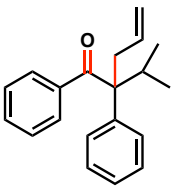
Following the *General Procedure B* with **160e**. The reaction was complete after 3 hr. The product was purified by silica gel flash column chromatography (3% diethyl ether/hexanes) to obtain 35.0 mg of a pale yellow oil (66% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.31 (m, 4H), 7.30 – 7.26 (m, 3H), 7.07 – 6.97 (m, 2H), 5.51 (dddd, *J* = 17.0, 10.2, 7.6, 6.9 Hz, 1H), 5.00 – 4.90 (m, 2H), 2.83 (ddt, *J* = 13.8, 7.7, 1.1 Hz, 1H), 2.74 (ddt, *J* = 13.7, 6.9, 1.3 Hz, 1H), 2.29 (s, 3H), 1.57 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.7, 144.0, 142.4, 134.2, 133.9, 129.9, 129.0, 128.9, 128.7, 126.9, 126.3, 118.4, 54.3, 44.9, 23.9, 21.5.

FT-IR (neat film NaCl): 3061, 3026, 2977, 2924, 1672, 1606, 1496, 1446, 1376, 1241, 1183, 966, 972, 916, 830, 745, 702, 597 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{19}H_{21}O$ 265.1587; Found 265.1588.



2-isopropyl-1,2-diphenylpent-4-en-1-one (161l)

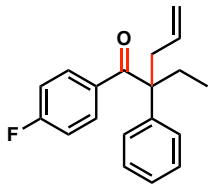
Following the *General Procedure B* with **160f** at 95 ºC. The reaction was complete after 3 hr. The product was purified by silica gel flash column chromatography (3% diethyl ether/hexanes) to obtain 23.0 mg of a pale yellow oil (41% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.40 (m, 2H), 7.37 – 7.26 (m, 4H), 7.23 – 7.12 (m, 4H), 5.60 (dddd, *J* = 17.1, 10.2, 7.6, 6.9 Hz, 1H), 5.01 – 4.78 (m, 2H), 3.22 (ddt, *J* = 14.4, 7.5, 1.2 Hz, 1H), 2.89 (ddt, *J* = 14.4, 6.9, 1.5 Hz, 1H), 2.65 (hept, *J* = 6.7 Hz, 1H), 0.82 (dd, *J* = 6.7, 3.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.8, 139.8, 137.0, 133.4, 131.7, 130.2, 128.9, 128.0, 127.8, 127.0, 118.3, 61.8, 38.7, 30.8, 30.4, 19.7, 17.4, 15.4.

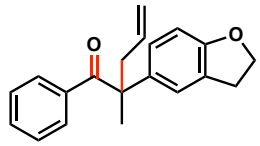
FT-IR (neat film NaCl): 3059, 3023, 2962, 2877, 1675, 1596, 1578, 1445, 1384, 1265, 1212, 1181, 916, 747, 705, 692, 647 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{20}H_{23}O$ 279.1743; Found 279.1739.



2-ethyl-1-(4-fluorophenyl)-2-phenylpent-4-en-1-one (161m)

Following the *General Procedure B* with **160g**. The reaction was complete after 3 hr. The product was purified by silica gel flash column chromatography (3% diethyl ether/hexanes) to obtain 38.0 mg of a pale yellow oil (68% yield). Spectra match reported literature.[76]



2-(2,3-dihydrobenzofuran-5-yl)-2-methyl-1-phenylpent-4-en-1-one (161n)

Following the *General Procedure B* with **160h**. The reaction was complete after 3 hr. The product was purified by silica gel flash column chromatography (7% diethyl ether/hexanes)

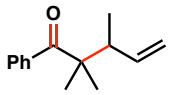
to obtain 41.2 mg of a pale yellow oil (71% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.42 (m, 2H), 7.41 – 7.34 (m, 1H), 7.23 (ddt, *J* = 7.9, 6.7, 1.2 Hz, 2H), 7.14 – 7.01 (m, 2H), 6.78 (d, *J* = 8.3 Hz, 1H), 5.52 (dddd, *J* = 17.1, 10.2, 7.7, 6.9 Hz, 1H), 5.04 – 4.82 (m, 2H), 4.58 (t, *J* = 8.7 Hz, 2H), 3.24 – 3.14 (m, 2H), 2.79 (ddt, *J* = 13.7, 7.6, 1.1 Hz, 1H), 2.71 (ddt, *J* = 13.7, 6.8, 1.3 Hz, 1H), 1.52 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.7, 159.2, 137.2, 135.4, 134.4, 131.6, 129.6, 128.1, 127.9, 125.8, 123.1, 118.3, 109.6, 71.5, 53.8, 44.9, 29.9, 23.9.

FT-IR (neat film NaCl): 3072, 2979, 2941, 2361, 2342, 2292, 2252, 1674, 1639, 1614, 1596, 1493, 1445, 1374, 1235, 1183, 1110, 1039, 982, 972, 943, 918, 822, 798, 735, 716, 695, 660, 626 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{20}H_{21}O_2$ 293.1536; Found 293.1543.



2,2,3-trimethyl-1-phenylpent-4-en-1-one (164a)

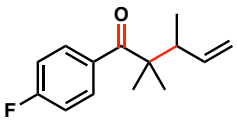
Following the *General Procedure A* with **118b** and **163a**. The reaction was complete after 2 hr. The product was purified by silica gel flash column chromatography (15–18% benzene/hexanes) to obtain 30.5 mg of a pale yellow oil (75% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.62 (m, 2H), 7.48 – 7.43 (m, 1H), 7.42 – 7.37 (m, 2H), 5.75 (ddd, *J* = 17.0, 10.4, 8.1 Hz, 1H), 5.06 – 4.98 (m, 2H), 2.88 (dqt, *J* = 7.8, 6.8, 1.0 Hz, 1H), 1.26 (s, 3H), 1.22 (s, 3H), 0.97 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.7, 139.7, 130.8, 128.2, 127.7, 116.1, 50.9, 44.4, 24.1, 21.6, 15.4.

FT-IR (neat film NaCl): 3075, 2970, 2927, 2874, 1674, 1598, 1462, 1444, 1389, 1253, 1176, 1135, 1002, 965, 915, 714, 699 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{14}H_{19}O$ 203.1430; Found 203.1430.



1-(4-fluorophenyl)-2,2,3-trimethylpent-4-en-1-one (164b)

Following the *General Procedure A* with **114** and **163a**. The reaction was complete after 4.5 hr. The product was purified by silica gel flash column chromatography (3% diethyl ether/hexanes) to obtain 21.5 mg of a pale yellow oil (49% yield).

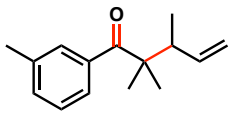
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.70 (m, 2H), 7.11 – 7.05 (m, 2H), 5.73 (ddd, *J* = 17.1, 10.4, 8.2 Hz, 1H), 5.06 – 4.96 (m, 2H), 2.86 (dqt, *J* = 7.8, 6.8, 1.0 Hz, 1H), 1.26 (s, 3H), 1.22 (s, 3H), 0.96 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 207.5, 164.3 (d, *J* = 252.2 Hz), 139.5, 135.3 (d, *J* = 3.5 Hz), 130.6 (d, *J* = 8.7 Hz), 116.2, 115.3 (d, *J* = 21.4 Hz), 50.9, 44.6, 24.0, 21.8, 15.4.

^{19}F NMR (282 MHz, $CDCl_3$) δ -108.5.

FT-IR (neat film NaCl): 3076, 2974, 2935, 2876, 1674, 1600, 1506, 1463, 1236, 1158, 967, 590 cm^{-1}.

HR-MS (ESI) m/z: [M+Na]+ Calculated for $C_{14}H_{17}FNaO$ 243.1156; Found. 243.1162.



2,2,3-trimethyl-1-(*m*-tolyl)pent-4-en-1-one (164c)

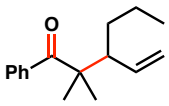
Following the *General Procedure A* with **162** and **163a**. The reaction was complete after 2.5 hr. The product was purified by silica gel flash column chromatography (3% diethyl ether/hexanes) to obtain 33.3 mg of a pale yellow oil (77% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.39 (m, 2H), 7.29 – 7.26 (m, 2H), 5.75 (ddd, *J* = 16.9, 10.3, 8.1 Hz, 1H), 5.07 – 4.98 (m, 2H), 2.88 (dqt, *J* = 7.8, 6.8, 1.0 Hz, 1H), 2.38 (s, 3H), 1.25 (s, 3H), 1.20 (s, 3H), 0.97 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 210.0, 139.8, 138.0, 131.5, 128.4, 127.9, 124.6, 116.1, 50.9, 44.3, 24.2, 21.63, 21.61, 15.4.

FT-IR (neat film NaCl): 3076, 2974, 2934, 2876, 1673, 1602, 1464, 1388, 1261, 1161, 1132, 999, 975, 916, 846, 749, 698, 531 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{15}H_{21}O$ 217.1587; Found 217.1585.



2,2-dimethyl-1-phenyl-3-vinylhexan-1-one (164d)

Following the *General Procedure A* with **118b** and **163b**. The reaction was complete after 2 hr. The product was purified by silica gel flash column chromatography (15–18% benzene/hexanes) to obtain 37.1 mg of a pale yellow oil (81% yield).

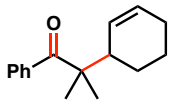
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.60 (m, 2H), 7.47 – 7.36 (m, 3H), 5.55 (ddd, *J* = 17.0, 10.2, 9.5 Hz, 1H), 5.14 – 4.95 (m, 2H), 2.61 (td, *J* = 9.8, 3.3 Hz, 1H), 1.37 – 1.26 (m, 2H), 1.25 (s, 3H), 1.24 – 1.22 (m, 1H), 1.21 (s, 3H), 1.09 – 0.99 (m, 1H), 0.77 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.8, 139.7, 138.2, 130.7, 128.2, 127.7, 118.1, 50.9, 32.1,

25.0, 21.4, 20.9, 13.9.

FT-IR (neat film NaCl): 3074, 2959, 2932, 2872, 1674, 1597, 1466, 1444, 1387, 1250, 1177, 1001, 974, 955, 916, 699 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{16}H_{23}O$ 231.1743; Found 231.1742.



2-(cyclohex-2-en-1-yl)-2-methyl-1-phenylpropan-1-one (164e)

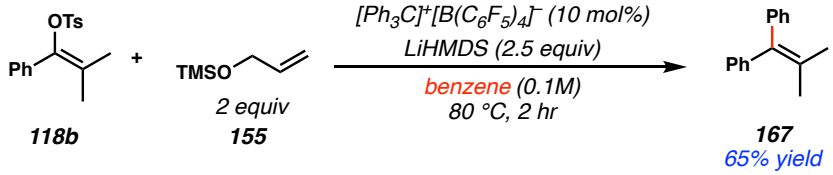
Following the *General Procedure A* with **118b** and **163c**. The reaction was complete after 4 hr. The product was purified by silica gel flash column chromatography (3% diethyl ether/hexanes) to obtain 28.5 mg of a pale yellow oil (62% yield). Spectra matched reported literature.[77]

3.6.5 Mechanistic Studies

3.6.5.1 Support for vinyl cation intermediacy

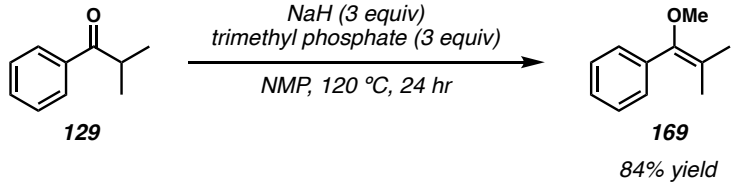
To a dram vial equipped with a magnetic stir bar was added $[Ph_3C]^+[B(C_6F_5)_4]^-$ catalyst (10 mol%), followed by LiHMDS (2.5 equiv), followed by benzene solvent (0.5 mL). To this mixture was then added neat silyl allyl ether **155** (2 equiv) followed by **118b** (1 equiv). The reaction was then sealed with a Teflon cap and heated for 2 hours at 80 ºC. Once the reaction was complete, the vial was removed from the glovebox. The reaction was diluted with diethyl ether and plugged through silica gel (pushing through with diethyl ether) and concentrated *in vacuo*. The yield was determined to be 65% yield by qNMR using nitromethane as an internal standard for **167** by comparing the NMR to the known

literature for **167**.[78]



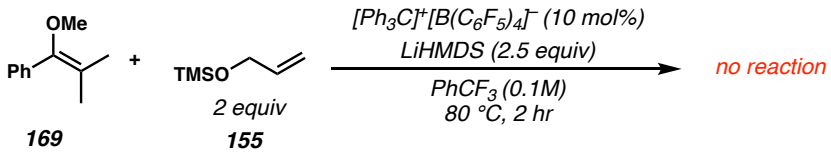
3.6.5.2 Activation of allyl ether:

First, (1-methoxy-2-methylprop-1-en-1-yl)benzene **169** was prepared according to a reported literature procedure[79]:

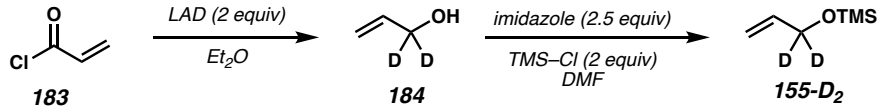


To a flame dried flask equipped with a stir bar was added 60% wt NaH (0.36 g, 9.0 mmol, 3 equiv), NMP (18 mL), and commercially available 2-methyl-1-phenylpropan-1-one **129** (0.45 mL, 3.0 mmol, 1 equiv). Trimethyl phosphate (1.0 mL, 9.0 mmol, 3 equiv) was then added. The flask was then equipped with a reflux condenser and heated at 120 ºC for 24 hours. After this time, the reaction was cooled to room temperature, and by TLC analysis (5% diethyl ether/hexanes) the reaction was complete with the formation of one more nonpolar spot. The reaction was then worked up by diluting with diethyl ether and washing with water. The aqueous layer was then extracted 2x with diethyl ether. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to obtain a crude oil, which was then purified by flash column chromatography using 2.5% diethyl ether/hexanes with 0.1% triethylamine to afford 407 mg (84% yield) of a colorless oil **169**. Spectra matched the reported literature.[79]

The mechanistic experiment was performed on a 0.050 mmol scale inside a well-kept glovebox. To a dram vial equipped with a magnetic stir bar was added $[Ph_3C]^+[B(C_6F_5)_4]^-$ catalyst (10 mol%), followed by LiHMDS (2.5 equiv), followed by $PhCF_3$ solvent (0.5 mL). To this mixture was then added neat **155** (2 equiv) followed by **169** (1 equiv). The reaction was then sealed with a Teflon cap and heated for 2 hours at 80 ºC. After 2 hours, the reaction was removed from the glovebox. By TLC analysis, no new product spots were apparent (5% diethyl ether/hexanes).



3.6.5.3 Claisen rearrangement with deuterated TMS allyl ether:



Allyl-1-d$_2$ alcohol (184) was first prepared according to a known literature procedure.[80] To a flame dried flask was added LAD (2.52 g, 0.64 equiv, 60.1 mmol) followed by anhydrous diethyl ether (130 mL), and this solution was cooled to 0 ºC. Neat acrolyl chloride **183** (8.50 g, 1 equiv, 93.9 mmol) was added dropwise to the LAD solution. After the addition was complete, the reaction was allowed to warm up to room temperature and stirred for 3.5 hours, and at this time starting material appeared to be consumed by TLC (visualization by $KMnO_4$ stain). The reaction was cooled back to 0 ºC, and 2.5 mL of

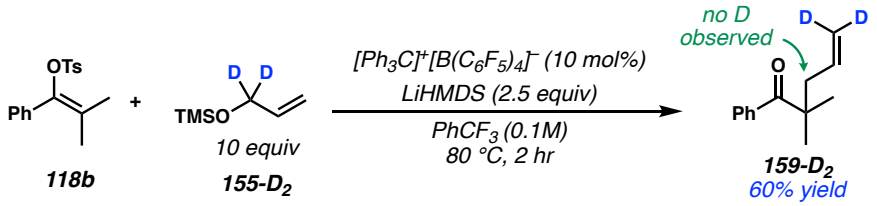
15% aq. NaOH was added dropwise. Then, 7.5 mL of H_2O was added dropwise. The reaction was then allowed to warm to room temperature and stir for an additional 15 minutes. $MgSO_4$ was added and stirred for 15 additional minutes. The reaction was then sonicated for 10 minutes and filtered. The solids were washed with twice with 25 mL of diethyl ether. The crude reaction was then carried forward to the protection step.

Next, ((allyl-1,1-*d*2)oxy)trimethylsilane **155-D$_2$** was prepared by the procedure for silyl ethers in section **3.6.3** (with slight modification). Assuming quantitative yield from the previous step, imidazole (15.2 g, 2.5 equiv, 223 mmol) was added to the allyl-1-d_2 alcohol (**184**) in ether. The reaction was cooled to 0 ºC and distilled TMSCl (24 mL, 2.0 equiv, 178 mmol) was added dropwise. After addition was complete, the reaction was warmed up to room temperature and stirred until starting material had been fully consumed (~2 hours). 25 mL water was charged dropwise to quench residual TMSCl. After stirring for 10 minutes, the aqueous layer was extracted with 3 x 25 mL pentane. The combined organic layers were washed with brine and dried over Na_2SO_4. Due to the volatility of the product, the crude mixture was concentrated *in vacuo* at 0 ºC to approximately ~50 mL. Then, the compound was purified via fractional distillation at 135 ºC to obtain **155-D$_2$**. To note, residual ether and silicon grease remained in the ether.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (dd, *J* = 17.1, 10.4 Hz, 1H), 5.25 (dd, *J* = 17.1, 1.8 Hz, 1H), 5.10 (dd, *J* = 10.4, 1.8 Hz, 1H), 0.13 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.0, 114.6, -0.5.

HR-MS (FI^+) m/z: [M] Calculated for $C_6H_{12}D_2OSi$ 132.0939; Found 132.0937.



The above mechanistic experiment was performed on a 0.050 mmol scale inside a well-kept glovebox. To a dram vial equipped with a magnetic stir bar was added $[Ph_3C]^+[B(C_6F_5)_4]^-$ catalyst (10 mol%), followed by LiHMDS (2.5 equivalents), followed by $PhCF_3$ solvent (0.5 mL). To this mixture was then added **155-D₂** (10.0 equiv) followed by vinyl tosylate **118b** (1 equiv). The reaction was then sealed with a Teflon cap and heated for 2 hours at 80 ºC. After 2 hours, the reaction was removed from the glovebox, and the crude reaction mixture was plugged through silica gel with diethyl ether and concentrated *in vacuo*. By qNMR, product **159-D₂** was obtained in 60% yield with no observation of other deuterated isomer.

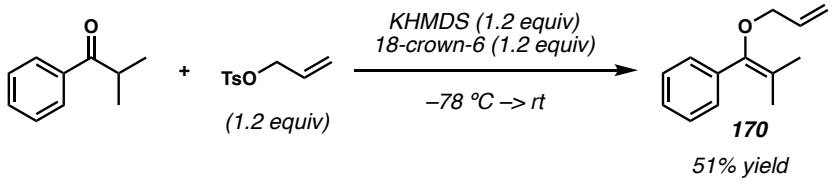
^{1}H NMR (400 MHz, $CDCl_3$) 7.69 – 7.62 (m, 2H), 7.48 – 7.36 (m, 3H), 5.77 – 5.65 (m, 1H), 2.49 (d, J = 7.3 Hz, 2H), 1.32 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.0, 139.2, 134.0, 130.9, 128.2, 127.8, 47.8, 45.0, 25.9.

HR-MS (FI^+) m/z: [M] Calculated for $C_{13}H_{14}D_2O$ 190.1327; Found 190.1328.

3.6.5.4 Neutral vs Cationic Claisen Rearrangement

Allyl vinyl ether **170** was prepared according to a known literature procedure[81]:



To a flame dried flask, 18-crown-6 (2.14 g, 1.2 equiv, 8.10 mmol) was added followed by THF (34 mL). The solution was sparged with argon for 10 minutes. To another flame dried flask, KHMDS (1.62 g, 1.2 equiv, 8.10 mmol) was added inside of a well-kept glovebox and then brought outside of the glovebox. Toluene (16.2 mL) was then added to the KHMDS, and this solution was then sparged with argon for 10 minutes. The solution of 18-crown-6 was then cooled to –78 ºC and the KHMDS solution was then added. Next, 2-methyl-1-phenylpropan-1-one was added dropwise. The yellow solution was allowed to stir at –78 ºC for 1 hour. Then, allyl 4-methylbenzenesulfonate (1.86 g, 1.3 equiv, 8.77 mmol) was added dropwise at –78 ºC. The reaction was allowed to slowly warm up to room temperature and stirred overnight. The reaction was then analyzed by TLC (5% diethyl/hexanes), which showed complete consumption of starting material with one major, more polar spot formed. The reaction was then worked up by first cooling to 0 ºC and adding saturated NH_4Cl. Diethyl ether was then added, and the reaction was extracted 3x. The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. The crude material was then purified by flash column chromatography in 3% diethyl/ether with 0.1% triethylamine. A pure oil (**170**) was obtained (650 mg, 51% yield).

^{1}H NMR (400 MHz, C_6D_6) δ 7.41 – 7.31 (m, 2H), 7.17 – 7.11 (m, 3H), 7.09 – 7.03 (m, 1H), 5.83 (ddt, *J* = 17.2, 10.7, 5.4 Hz, 1H), 5.17 (dq, *J* = 17.2, 1.8 Hz, 1H), 5.00 (dq, *J* = 10.4, 1.5 Hz, 1H), 3.91 (dt, *J* = 5.4, 1.6 Hz, 2H), 1.92 (s, 3H), 1.62 (s, 3H).

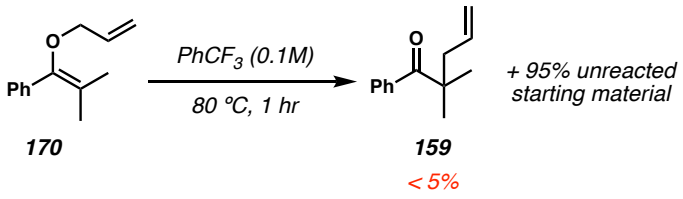
^{13}C NMR (101 MHz, C_6D_6) δ 148.3, 136.4, 135.3, 129.9, 128.3, 127.7, 116.2, 115.7, 70.1, 19.8, 18.1.

FT-IR (neat film NaCl): 3080, 3059, 3021, 2987, 2913, 2857, 1672, 1647, 1600, 1490, 1443, 1421, 1381, 1287, 1214, 1136, 1072, 1047, 1024, 985, 920, 883, 843, 775, 700, 559,

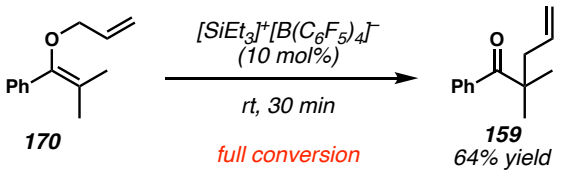
419 cm^{-1}.

HR-MS (FI^+) m/z: [M] Calculated for $C_{13}H_{16}O$ 188.1201; Found 188.1203.

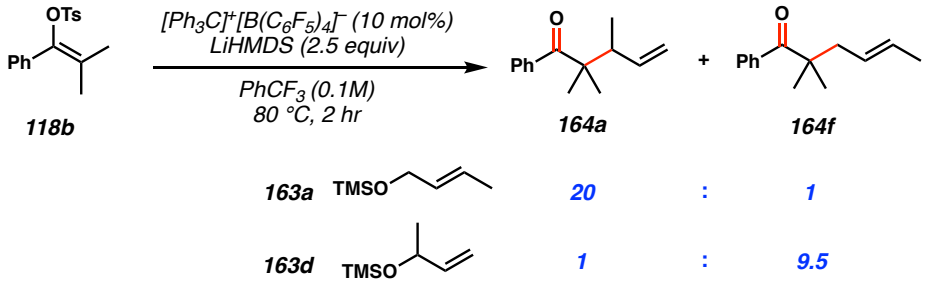
Neutral Claisen test: To a dram vial equipped with a magnetic stir bar inside the glovebox was added allyl vinyl ether **170** (9.5 mg, 0.050 mmol) followed by 0.5 mL of $PhCF_3$. The reaction was heat at 80 ºC for 1 hour. After the hour, the reaction was brought outside of the glovebox and concentrated *in vacuo*. By qNMR (nitromethane as internal standard), <5% of the rearranged product **159** was obtained with about 95% of **170** remaining.



Cationic Claisen test: To a dram vial equipped with a magnetic stir bar inside the glovebox was added $[Ph_3C]^+[B(C_6F_5)_4]^-$ (4.6 mg, 10 mol%). $PhCF_3$ (0.5 mL) was then added, followed by Et_3SiH (1.20 µL, 15 mol%). The mixture was then stirred at room temperature for 15 minutes. Then, allyl vinyl ether **170** (9.5 mg, 1 equiv, 0.050 mmol) was added and the reaction was allowed to stir at room temperature for 30 minutes. The reaction was brought outside of the glovebox, plugged through silica gel and washed with diethyl ether, and concentrated *in vacuo*. By qNMR (nitromethane as internal standard), the starting allyl vinyl ether **170** was fully consumed and **159** was observed in 64% yield.



3.6.5.5 Product distribution of substituted ethers:

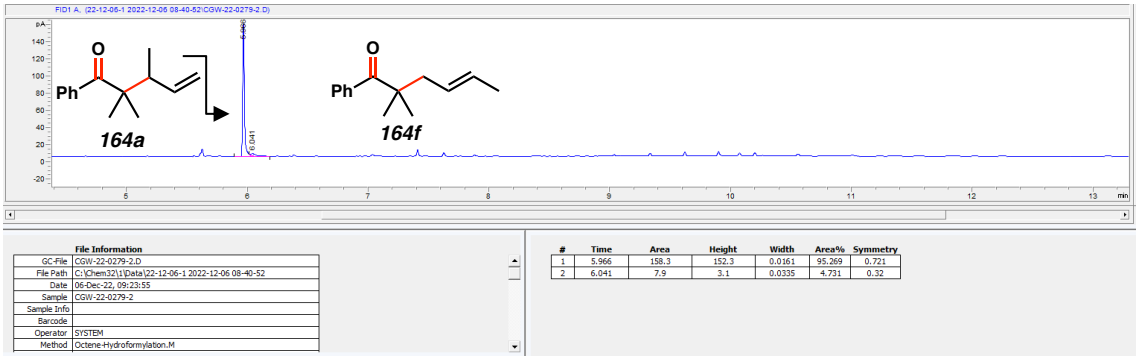


The following mechanistic experiment was performed on a 0.050 mmol scale inside a well-kept glovebox, and the two reactions were set up side by side. To a dram vial equipped with a magnetic stir bar was added $[Ph_3C]^+[B(C_6F_5)_4]^-$ catalyst (10 mol%), followed by LiHMDS (2.5 equiv), followed by $PhCF_3$ solvent (0.5 mL). To this mixture was then added either silyl ether **163a** (2 equiv) or **163d** (5 equiv, as it was determined that more equivalences lead to higher yield) followed by vinyl tosylate **118b** (1 equiv). The reactions were then sealed with a Teflon cap and heated for 2 hours at 80 ºC. After 2 hours, the reactions were removed from the glovebox, and aliquots were taken for GC analysis. The ratios were determined as indicated in the above scheme. To note, **163d** formed a small amount of the other olefin isomer (11:1 *E*:*Z*).

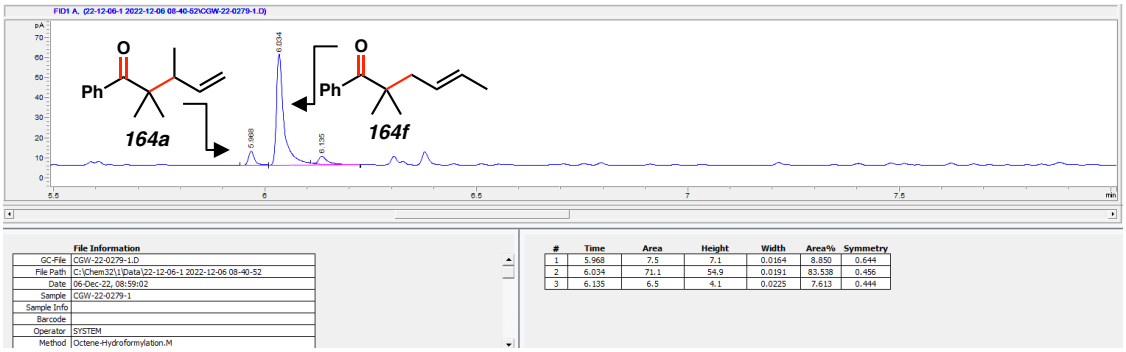
Product **164f** was further purified by HPLC (85:15 MeCN:H_2O). However, separating the E/Z mixture from product **164a** was unsuccessful. Product **164f** has been previously reported in the literature as a mixture of isomers[82], and thus could be correctly identified. The GC trace of the purified mixture thus contains the E/Z isomers in addition to product **164a**.

GC-FID traces:

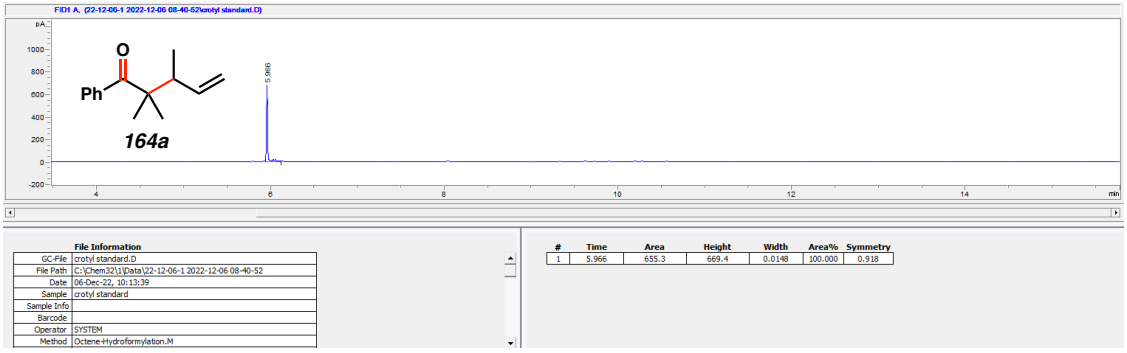
The following GC trace is of the crude reaction mixture using **silyl ether 163a:**



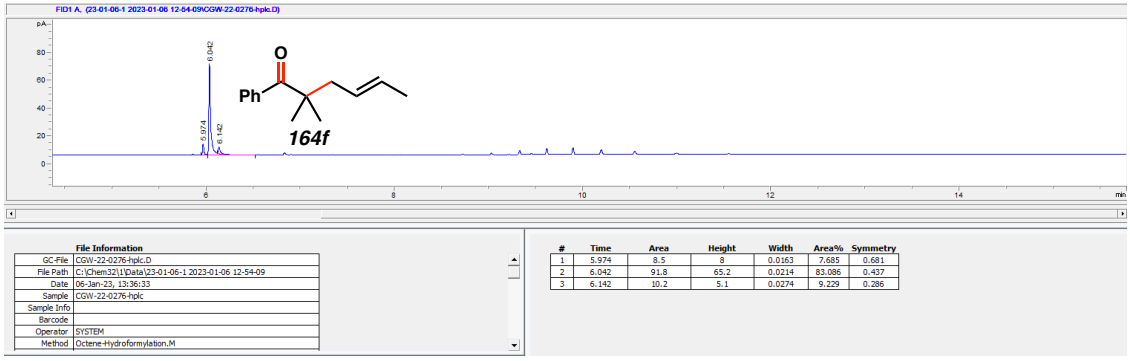
The following GC trace is of the crude reaction mixture using **silyl ether 163d**:



The following GC trace is of purified product **164a**:



The following GC trace is of purified product **164f** (with traces of minor *Z* isomer at 6.14 min and with traces of **164d** at 5.97 min):



3.7 NOTES AND REFERENCES

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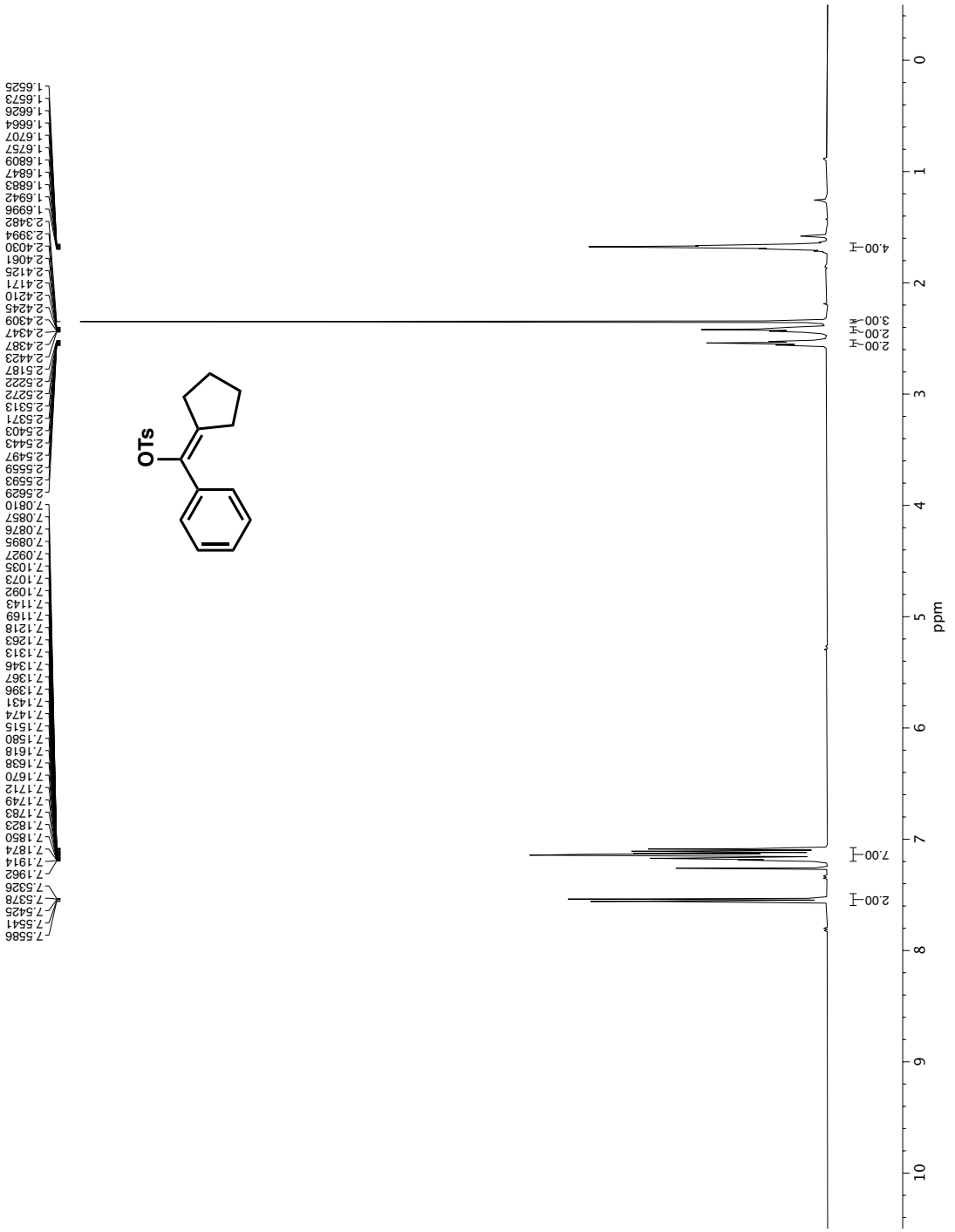
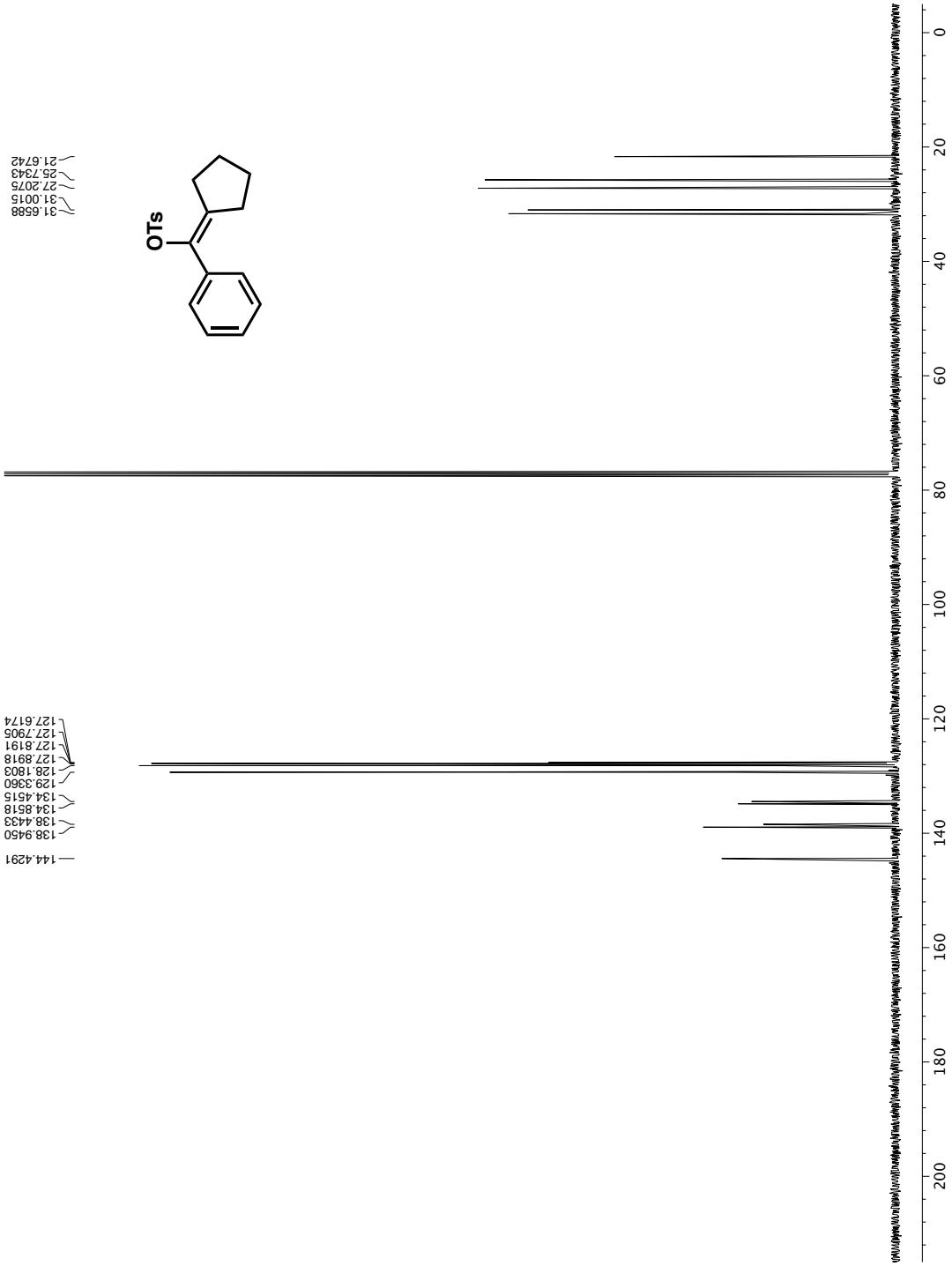
Appendix 2

Spectra Relevant to Chapter 3:

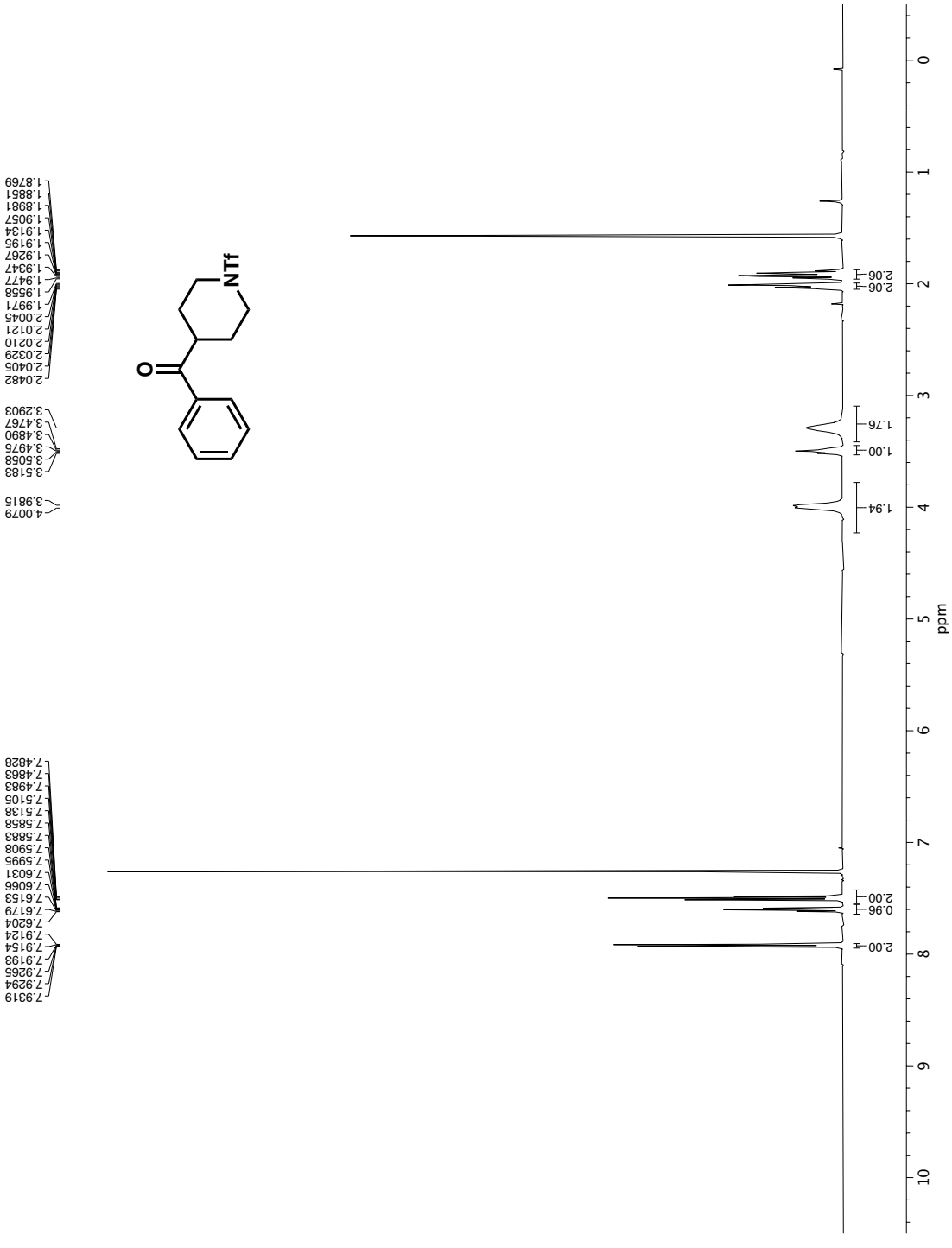
Cationic Claisen-Type Cascade Reactions Enabled by Vinyl Cation Capture



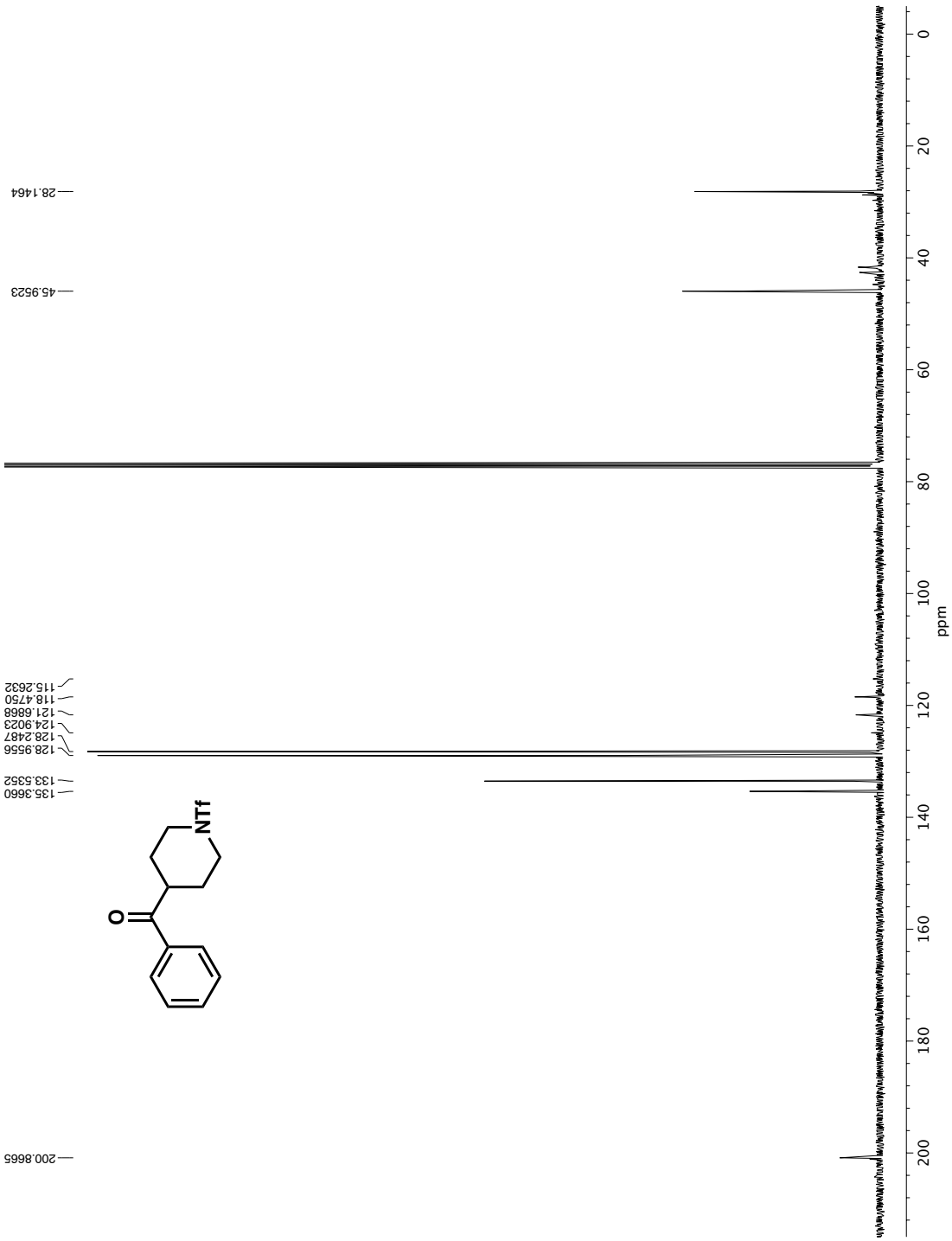
^{1}H NMR (400 MHz, $CDCl_3$) of compound **160a**.



^{13}C NMR (101 MHz, $CDCl_3$) of compound **160a**.

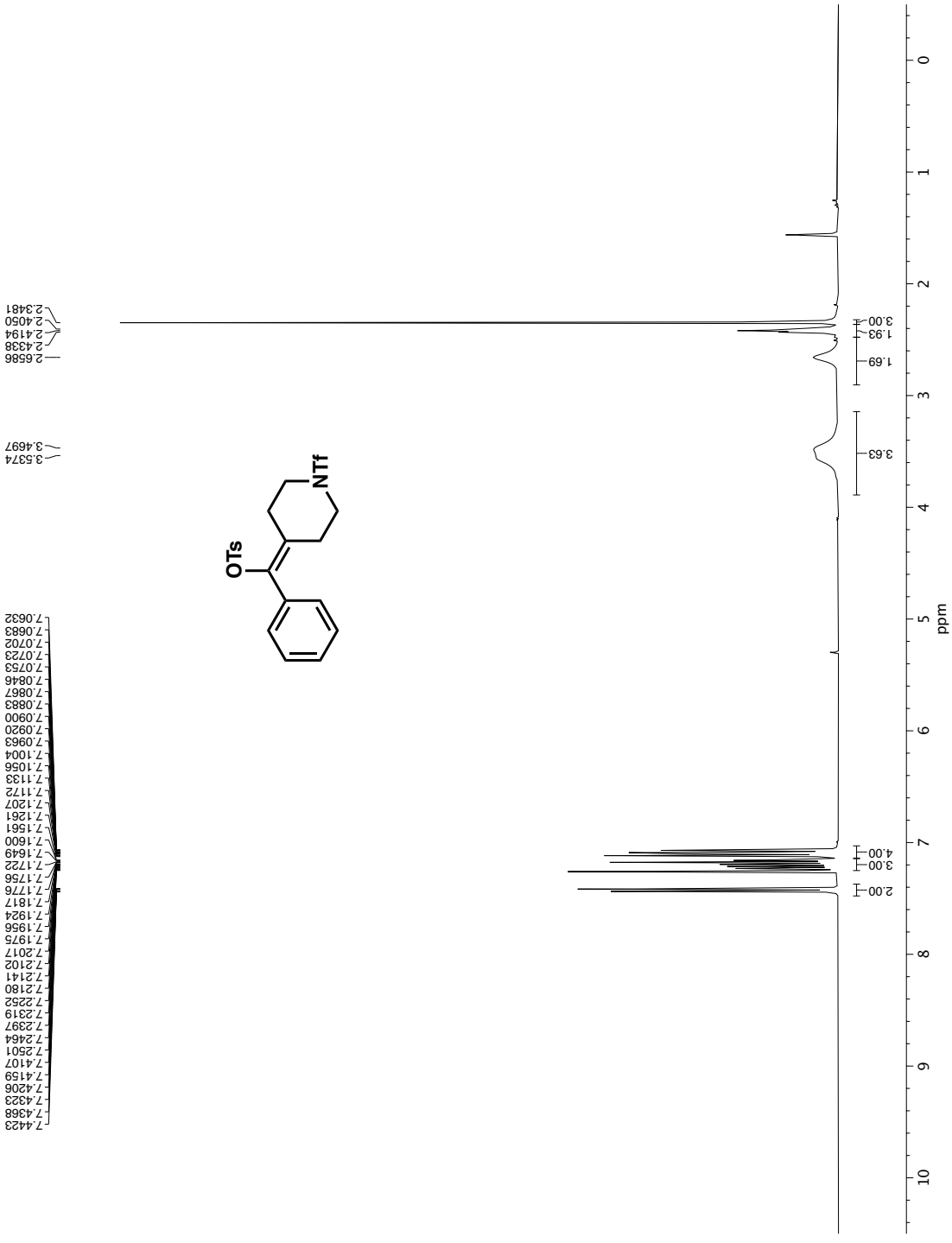


^{1}H NMR (500 MHz, $CDCl_3$) of compound **177**.

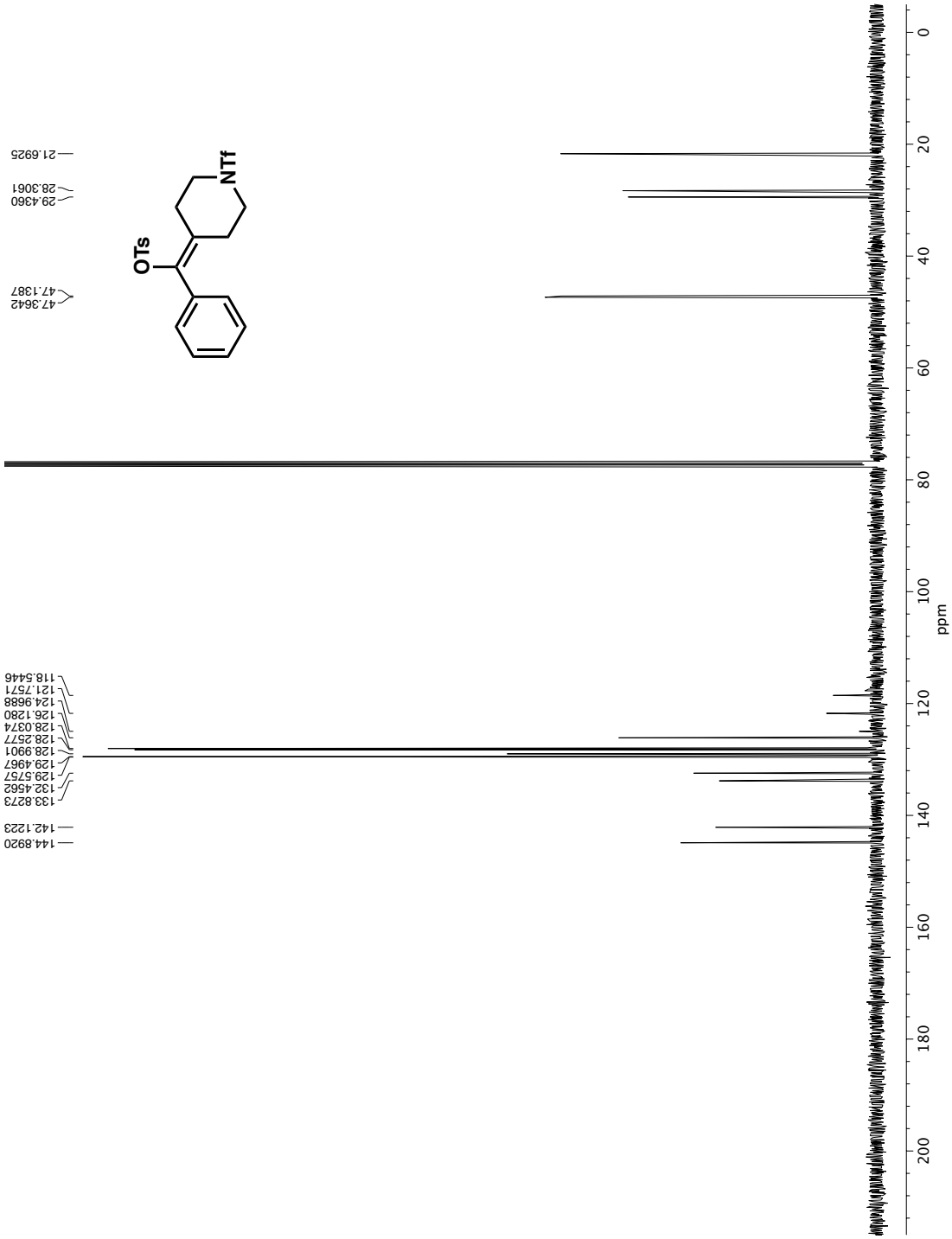


^{13}C NMR (101 MHz, $CDCl_3$) of compound **177**.

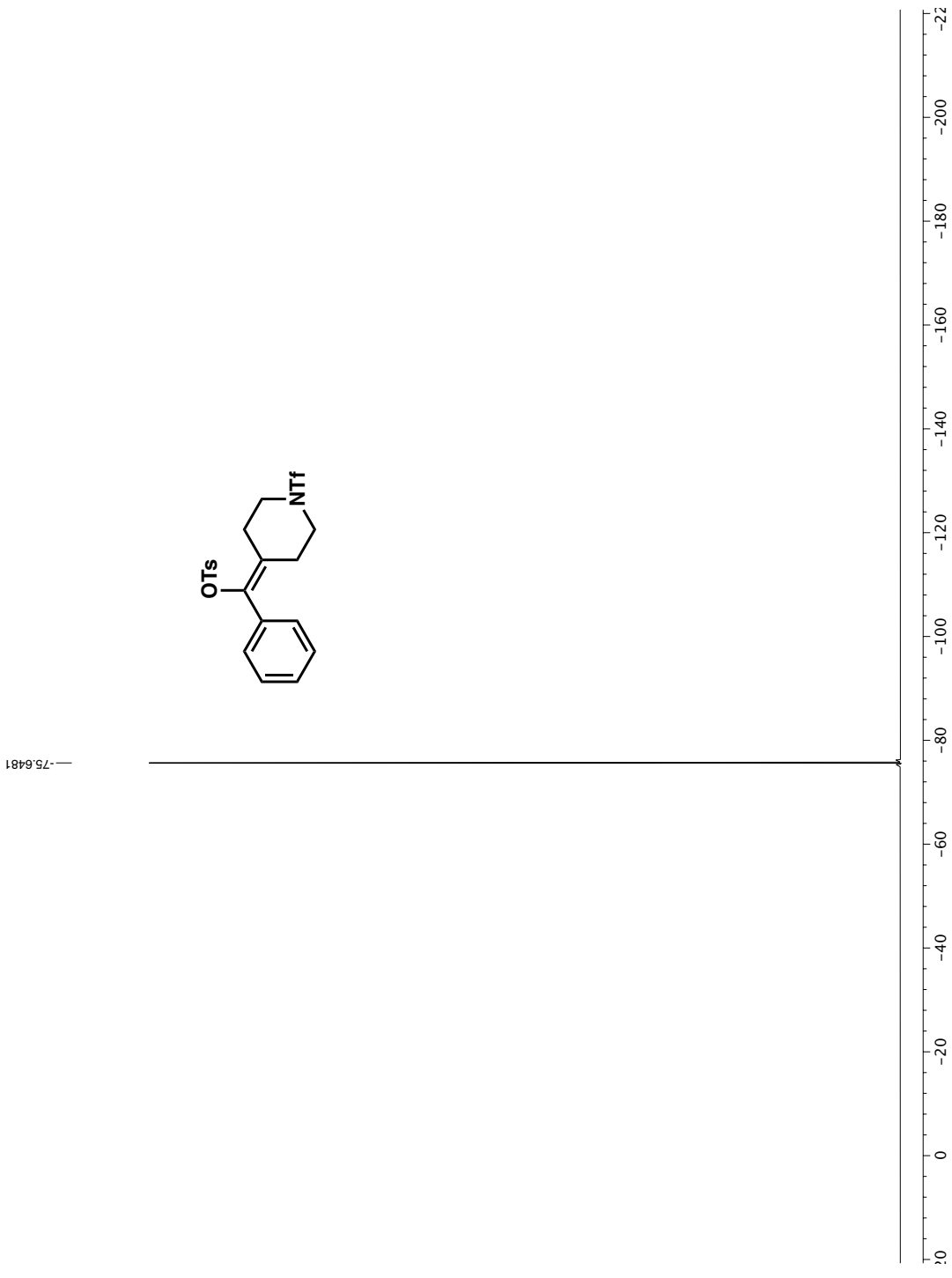
^{19}F NMR (376 MHz, $CDCl_3$) of compound **177**.



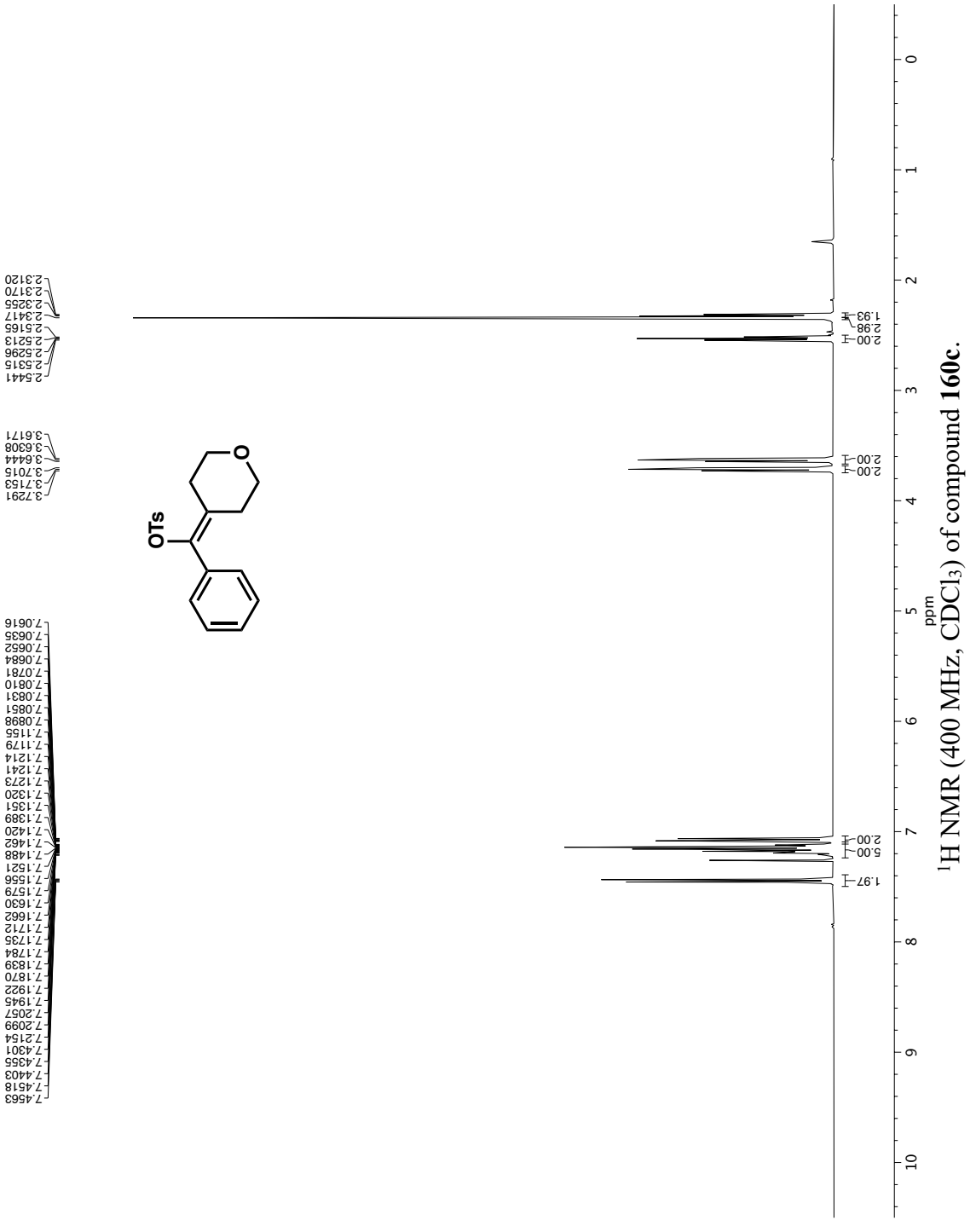
^{1}H NMR (400 MHz, $CDCl_3$) of compound **160b**.



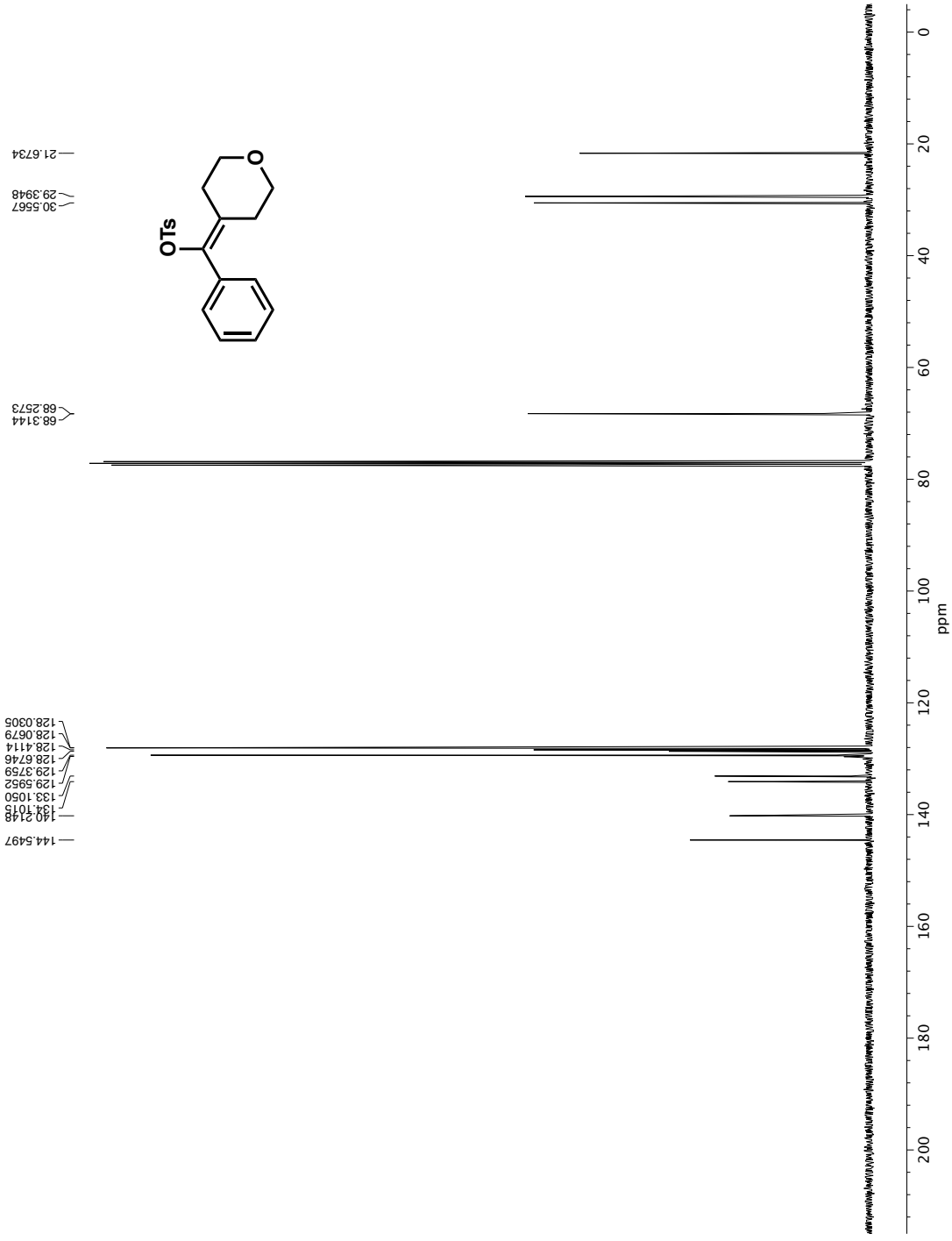
^{13}C NMR (101 MHz, $CDCl_3$) of compound **160b**.



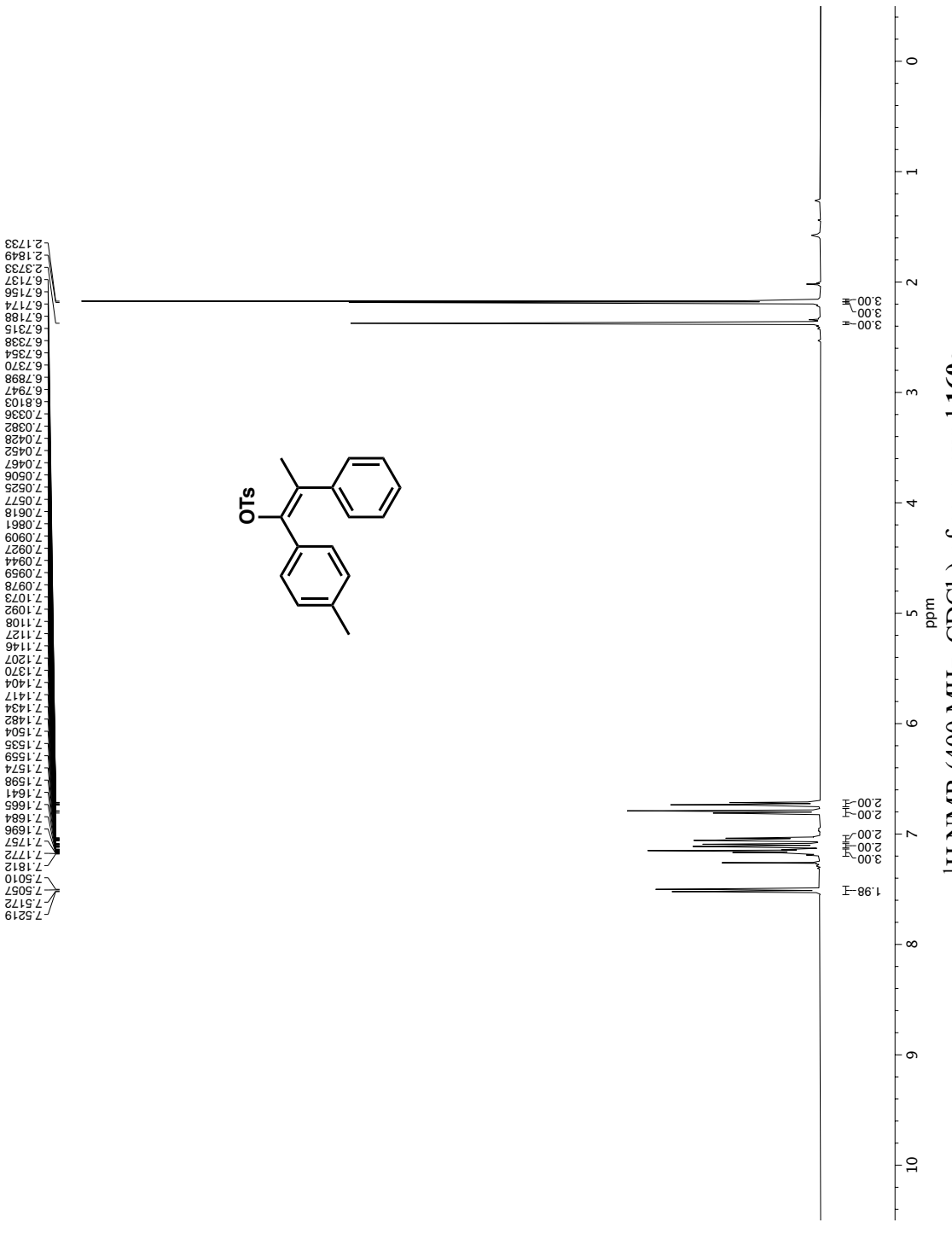
^{19}F NMR (376 MHz, $CDCl_3$) of compound **160b**.



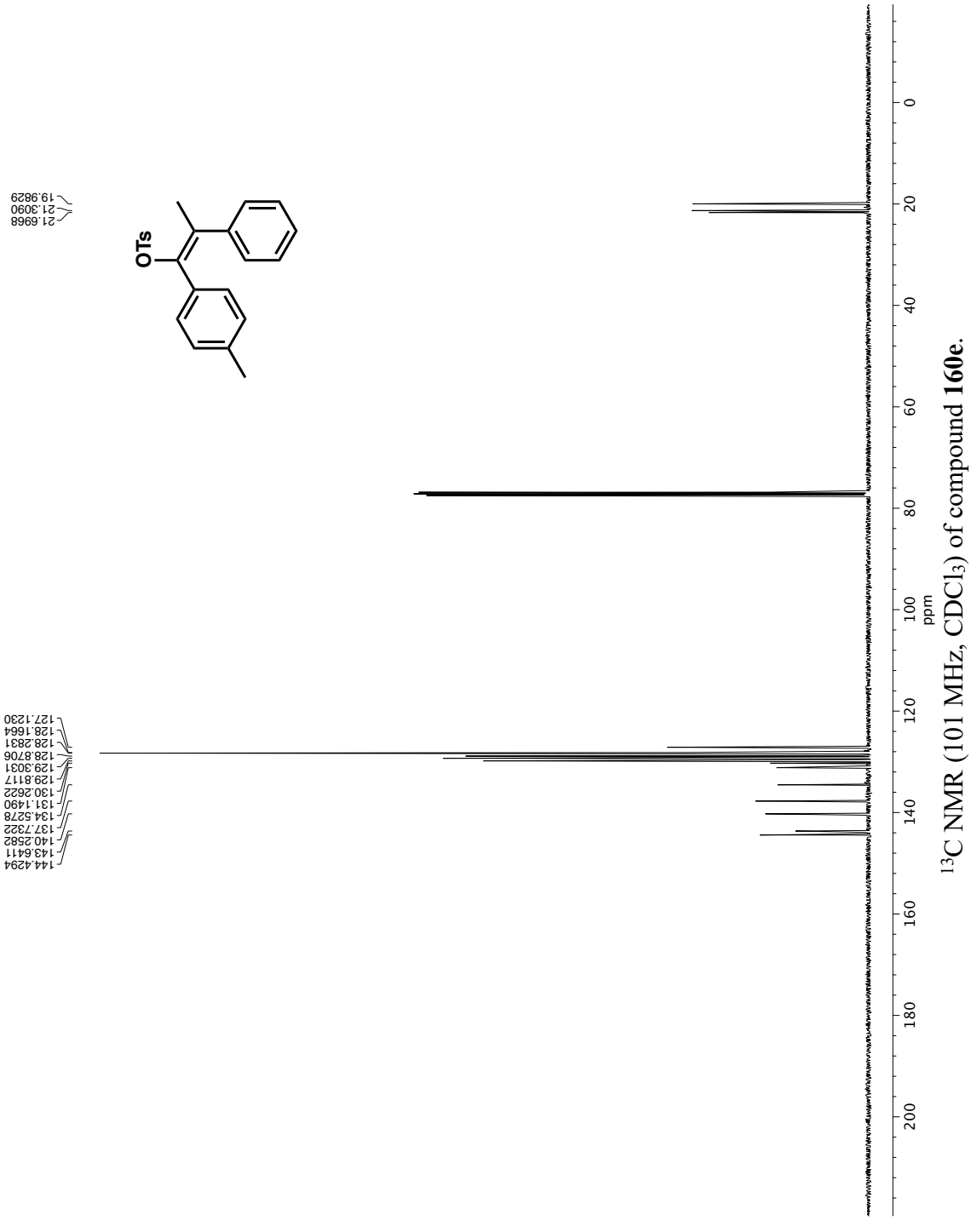
^{1}H NMR (400 MHz, $CDCl_3$) of compound **160c**.



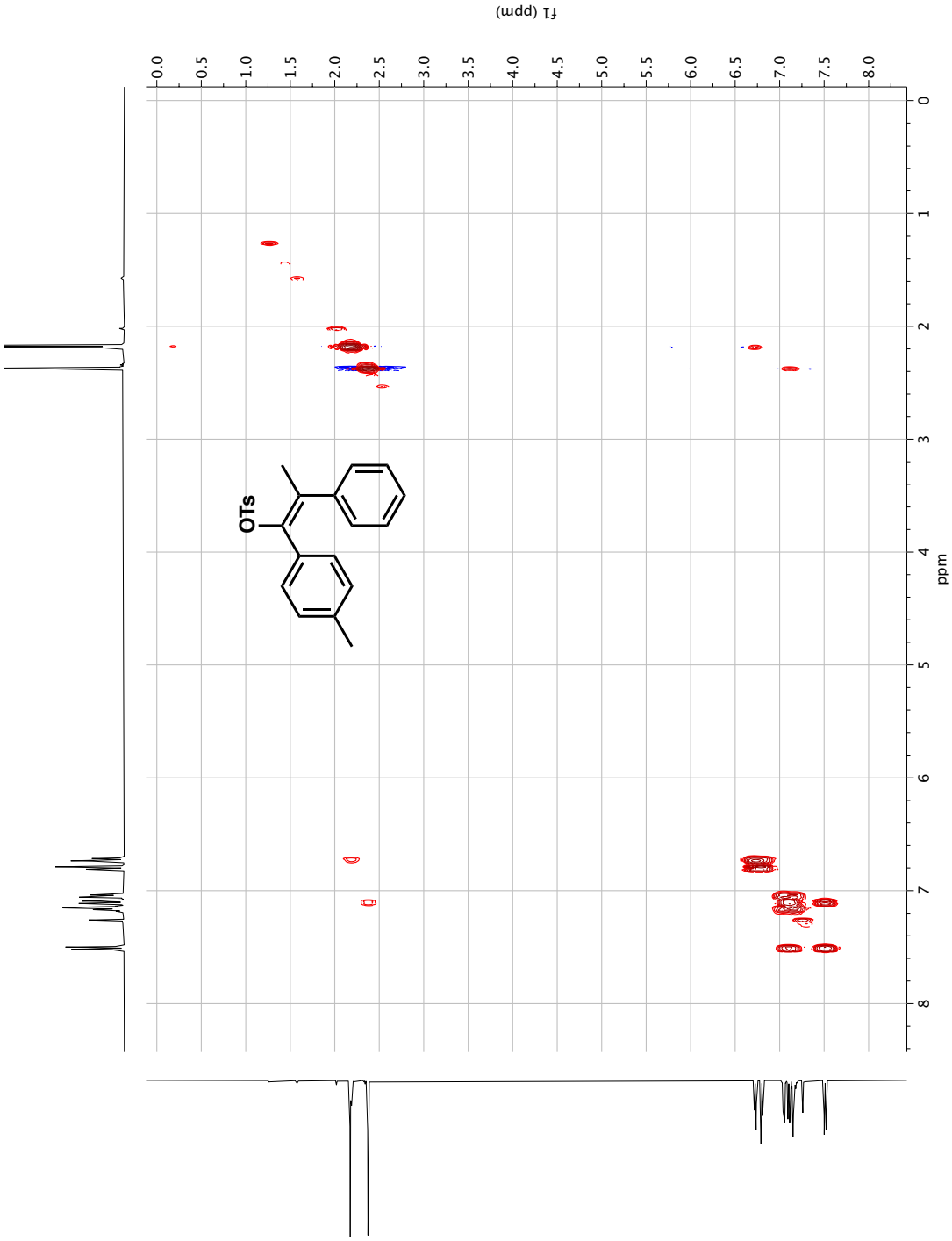
^{13}C NMR (101 MHz, $CDCl_3$) of compound **160c**.



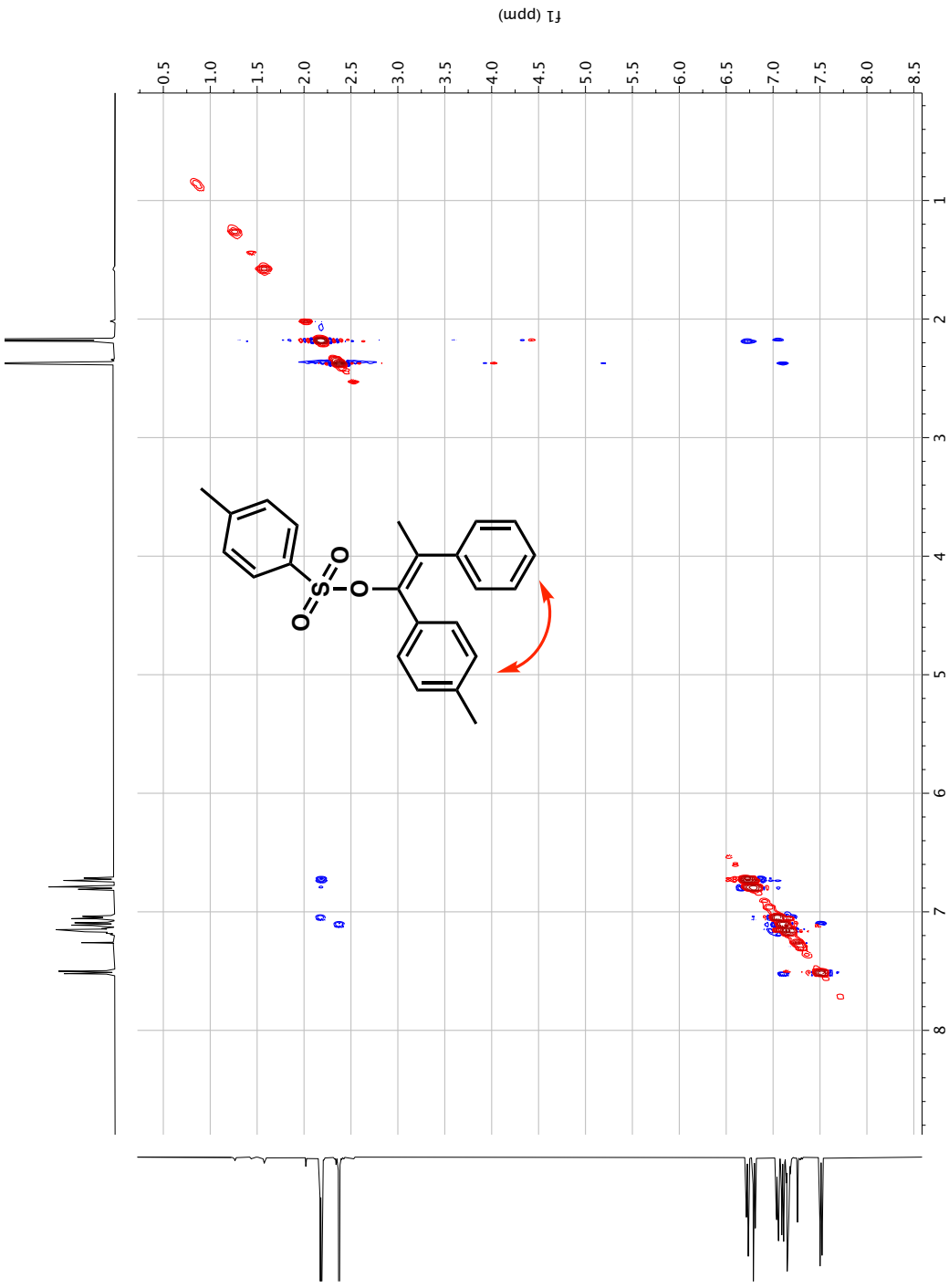
^{1}H NMR (400 MHz, $CDCl_3$) of compound **160e**.



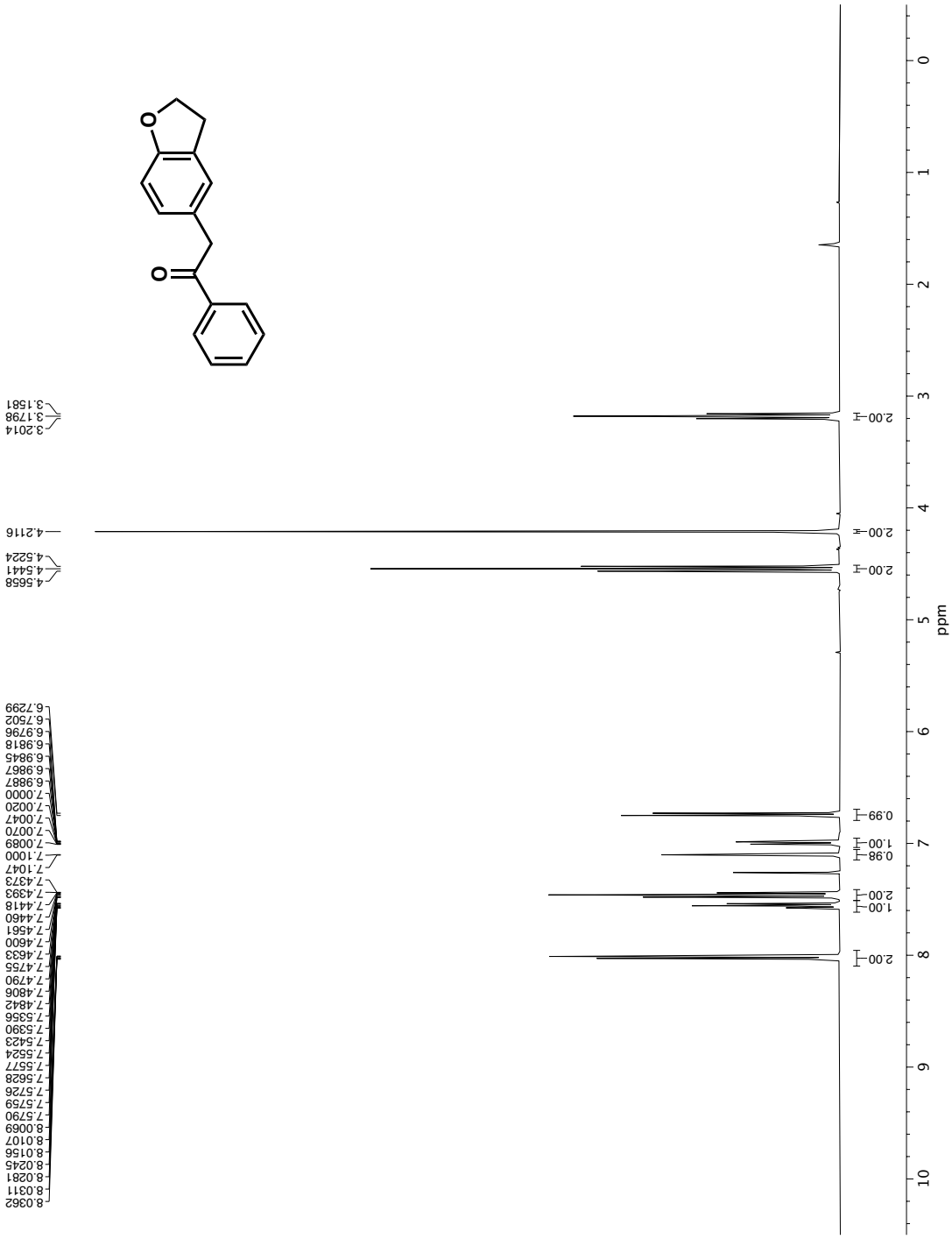
^{13}C NMR (101 MHz, $CDCl_3$) of compound **160e**.



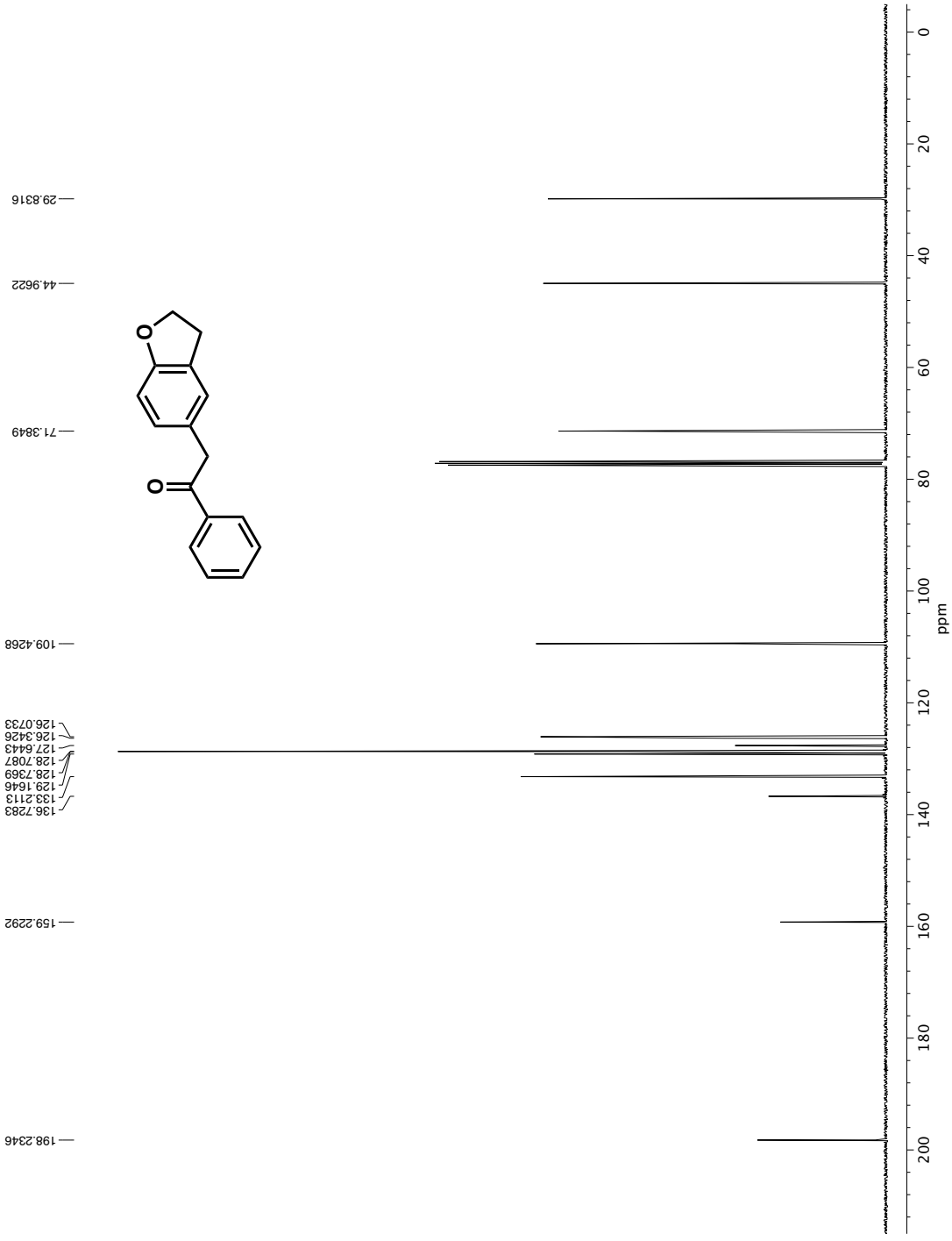
COSY (400 MHz, $CDCl_3$) of compound **160e**.



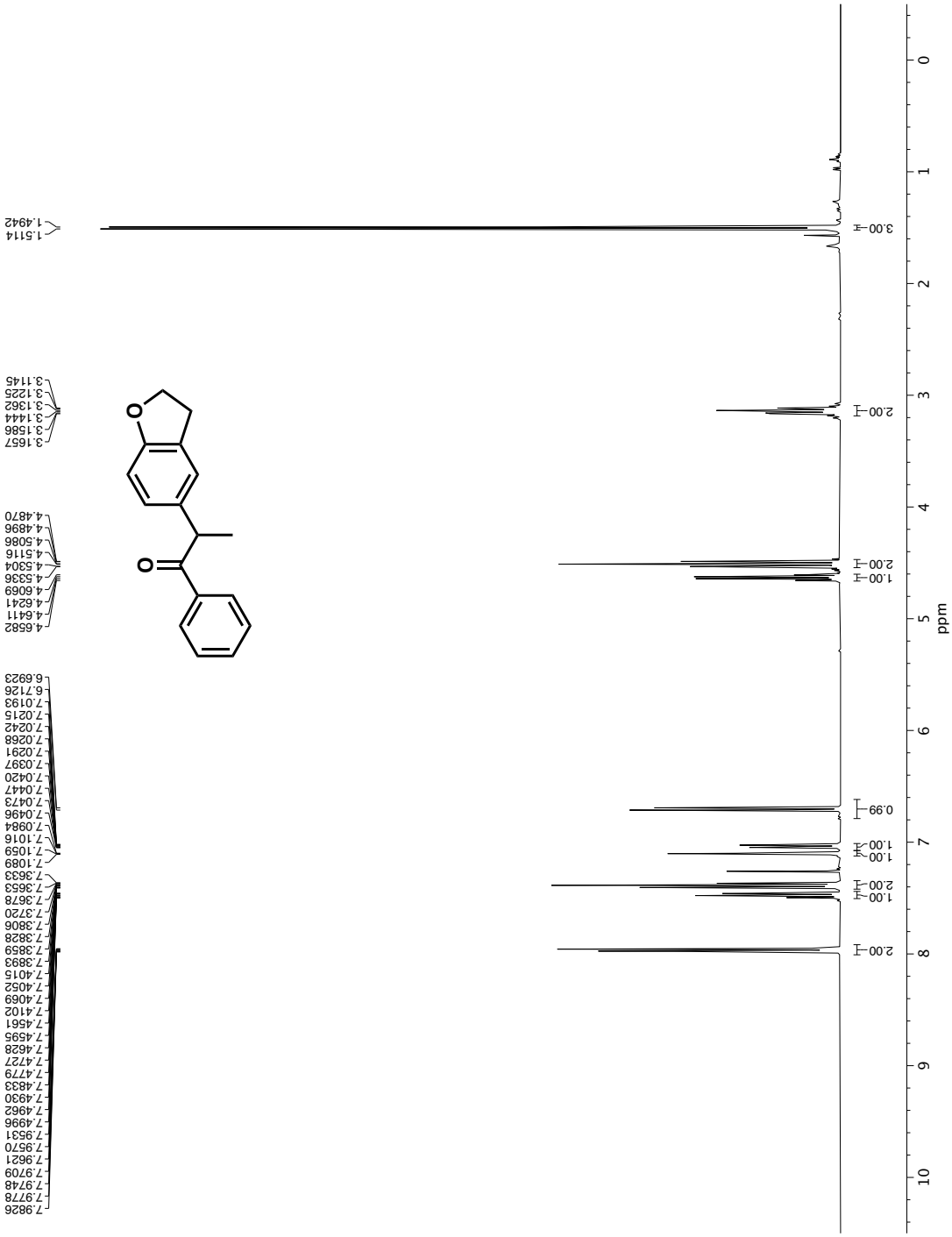
NOESY (400 MHz, $CDCl_3$) of compound **160e**.



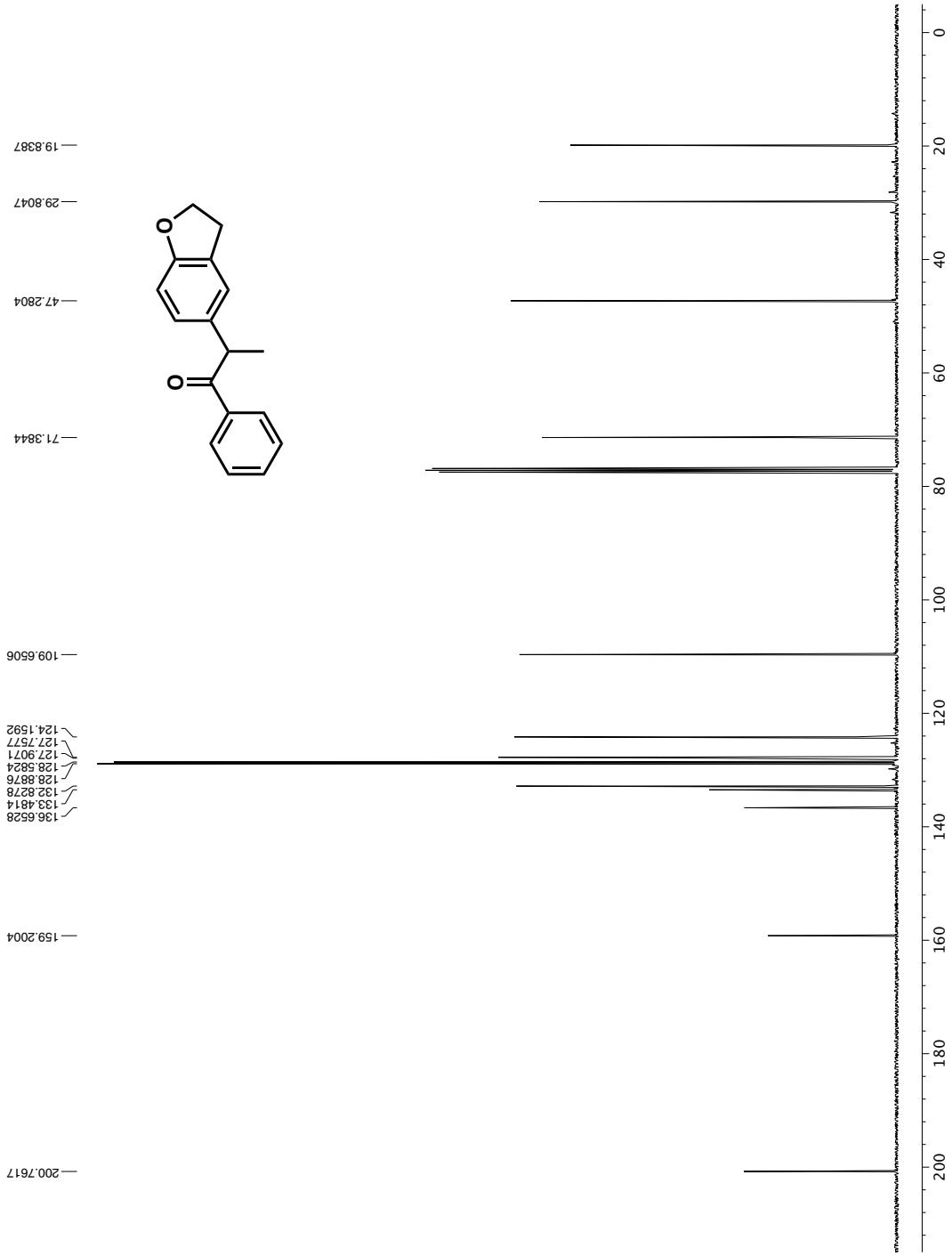
^{1}H NMR (400 MHz, $CDCl_3$) of compound **181**.



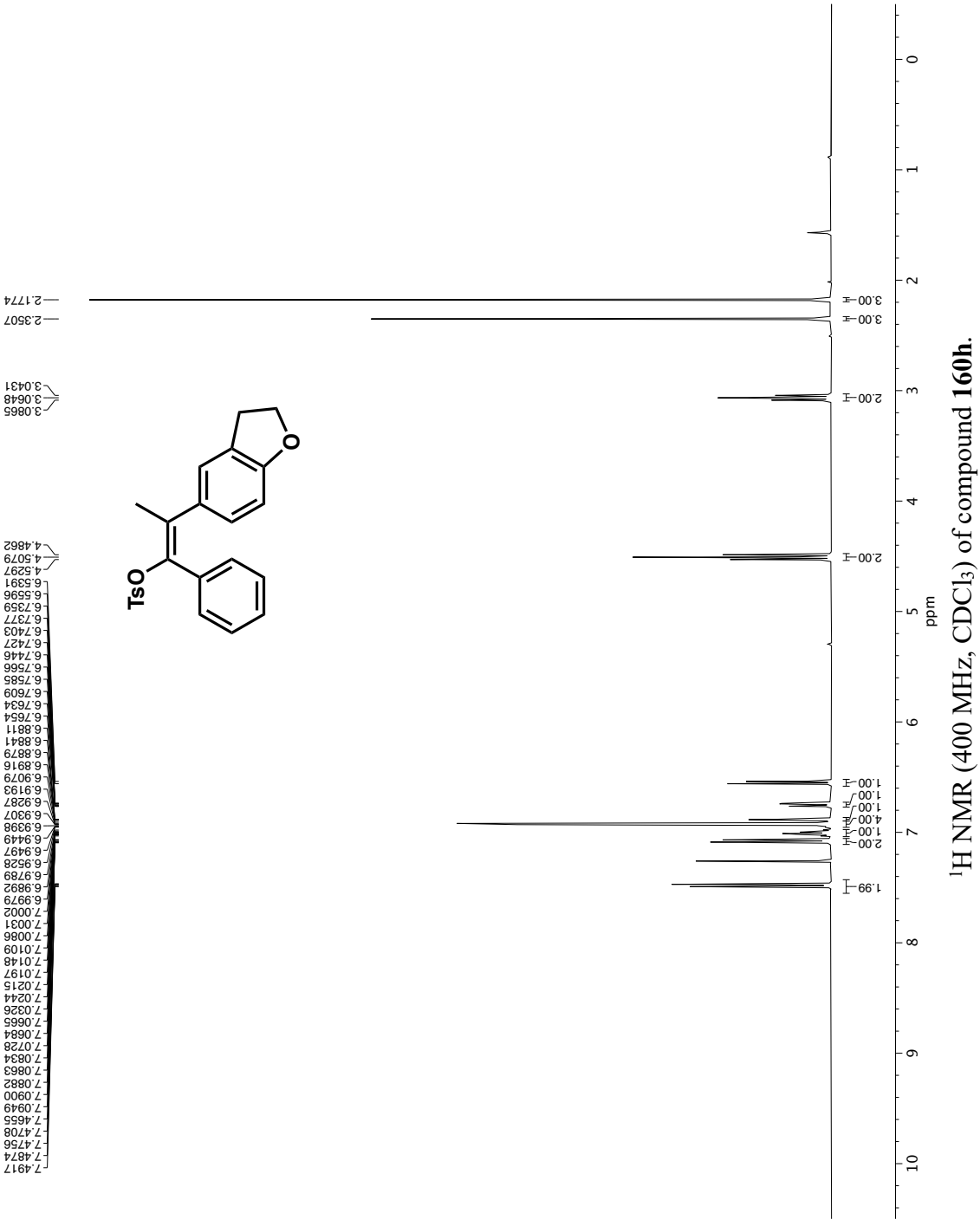
^{13}C NMR (101 MHz, $CDCl_3$) of compound **181**.



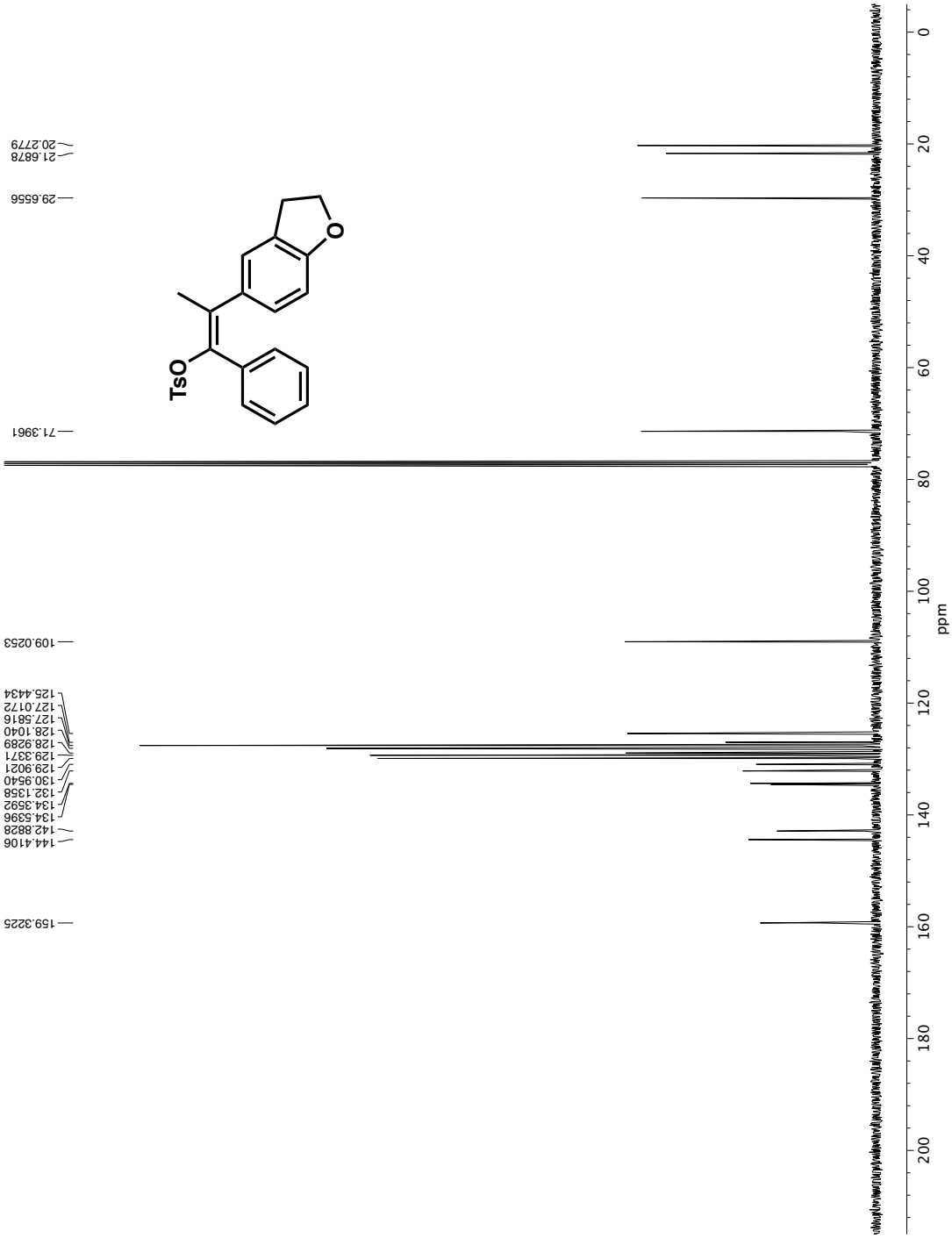
^{1}H NMR (400 MHz, $CDCl_3$) of compound **182**.



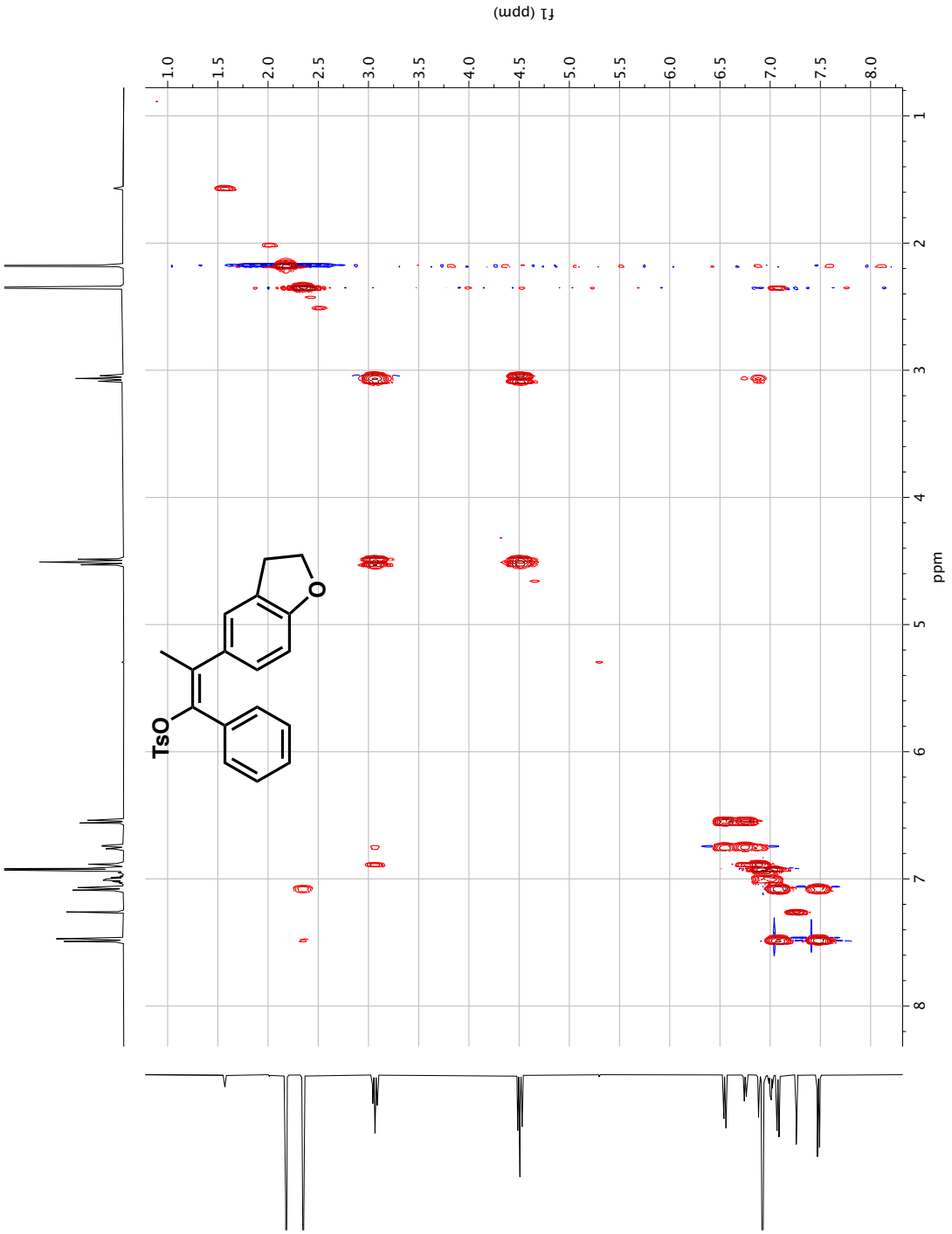
^{13}C NMR (101 MHz, $CDCl_3$) of compound **182**.



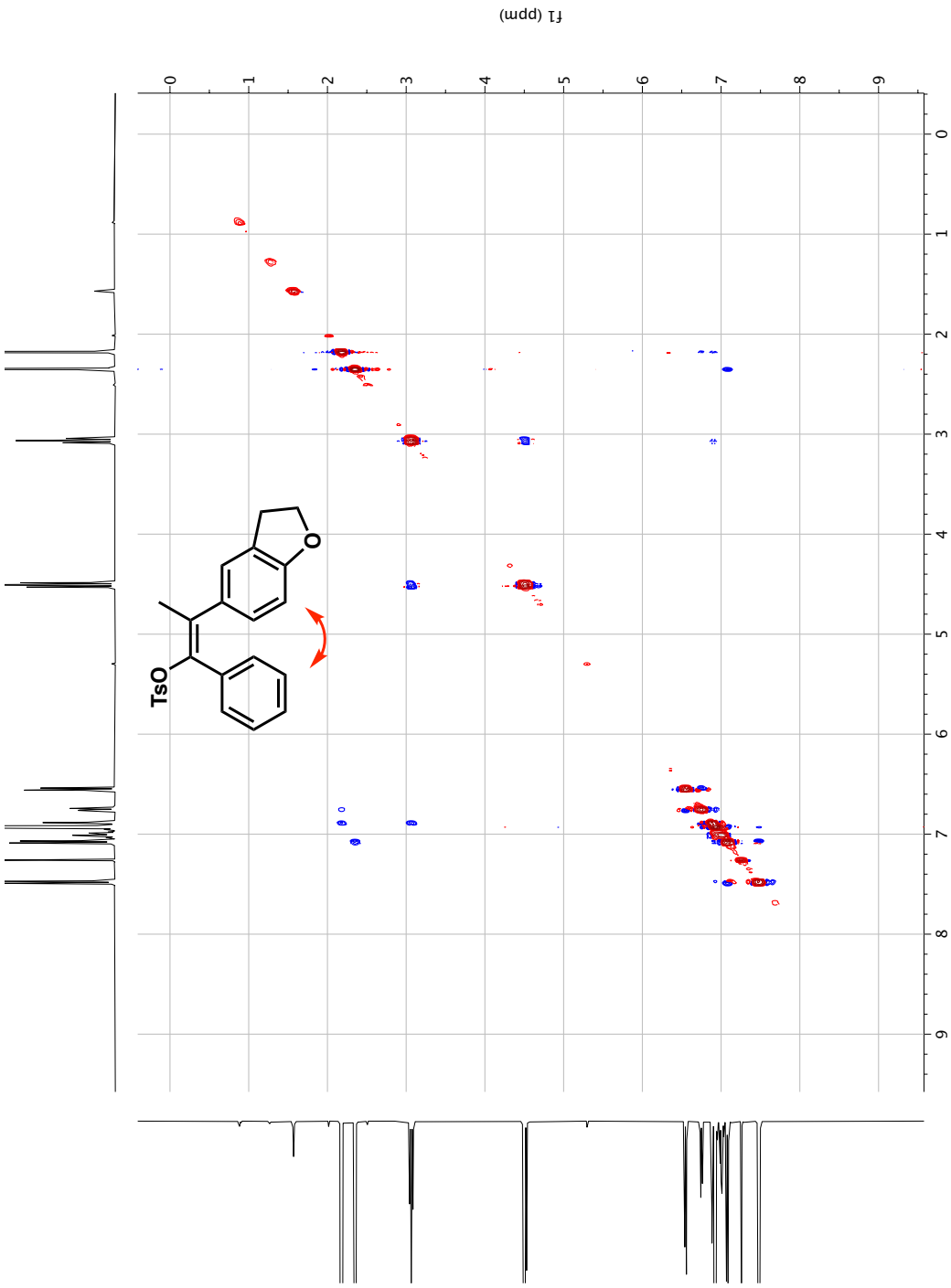
^{1}H NMR (400 MHz, $CDCl_3$) of compound **160h**.



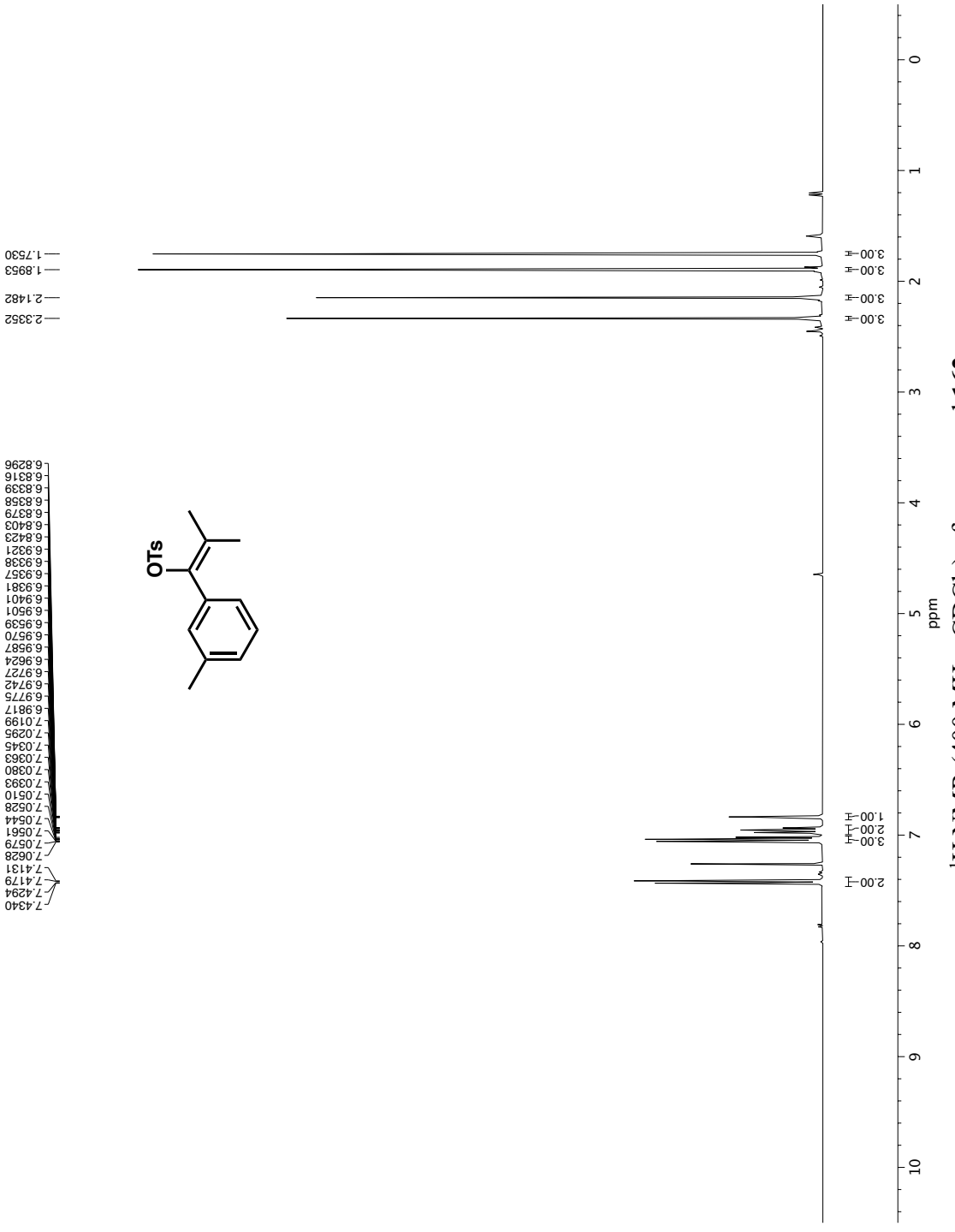
^{13}C NMR (101 MHz, $CDCl_3$) of compound **160h**.



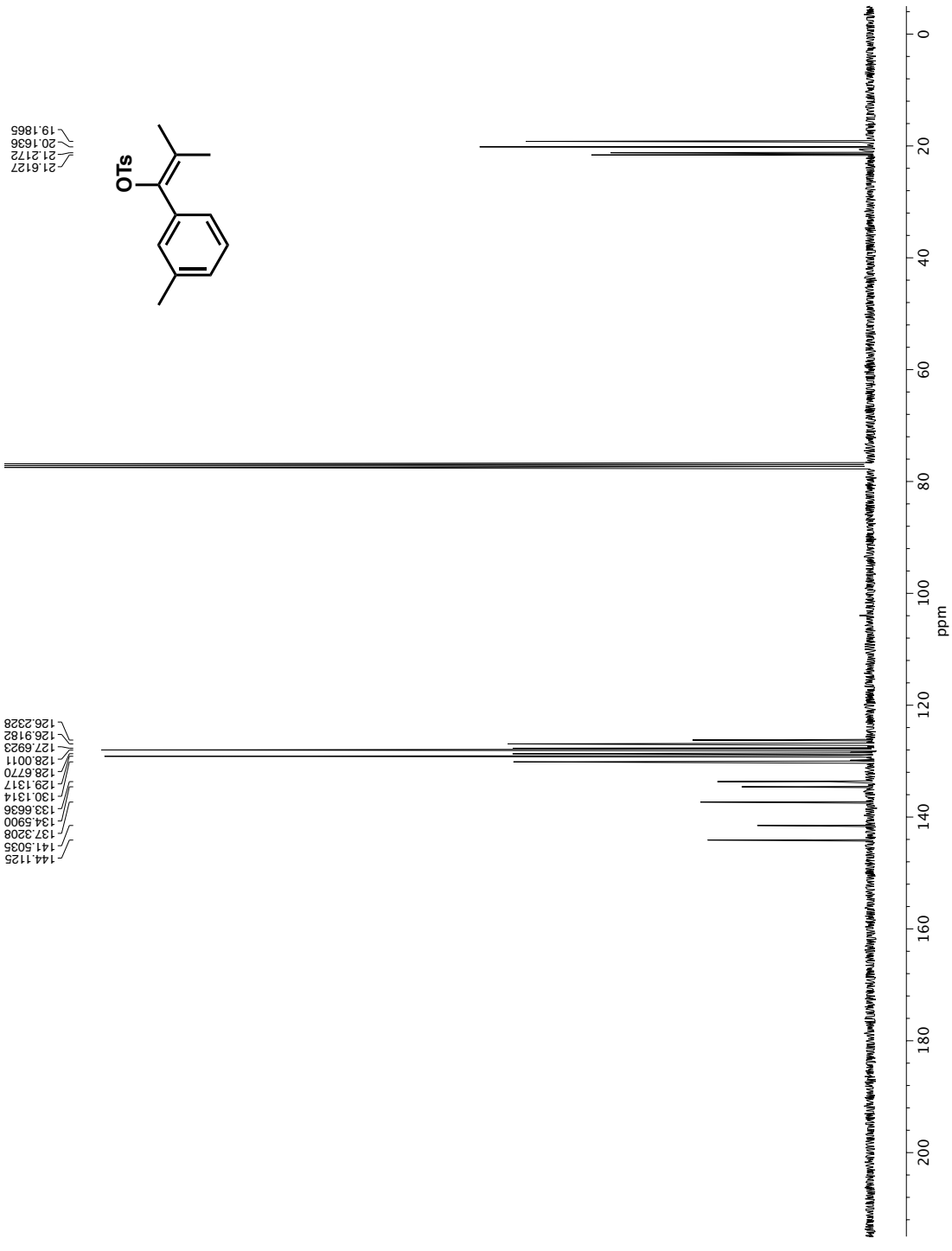
COSY (400 MHz, $CDCl_3$) of compound **160h.**



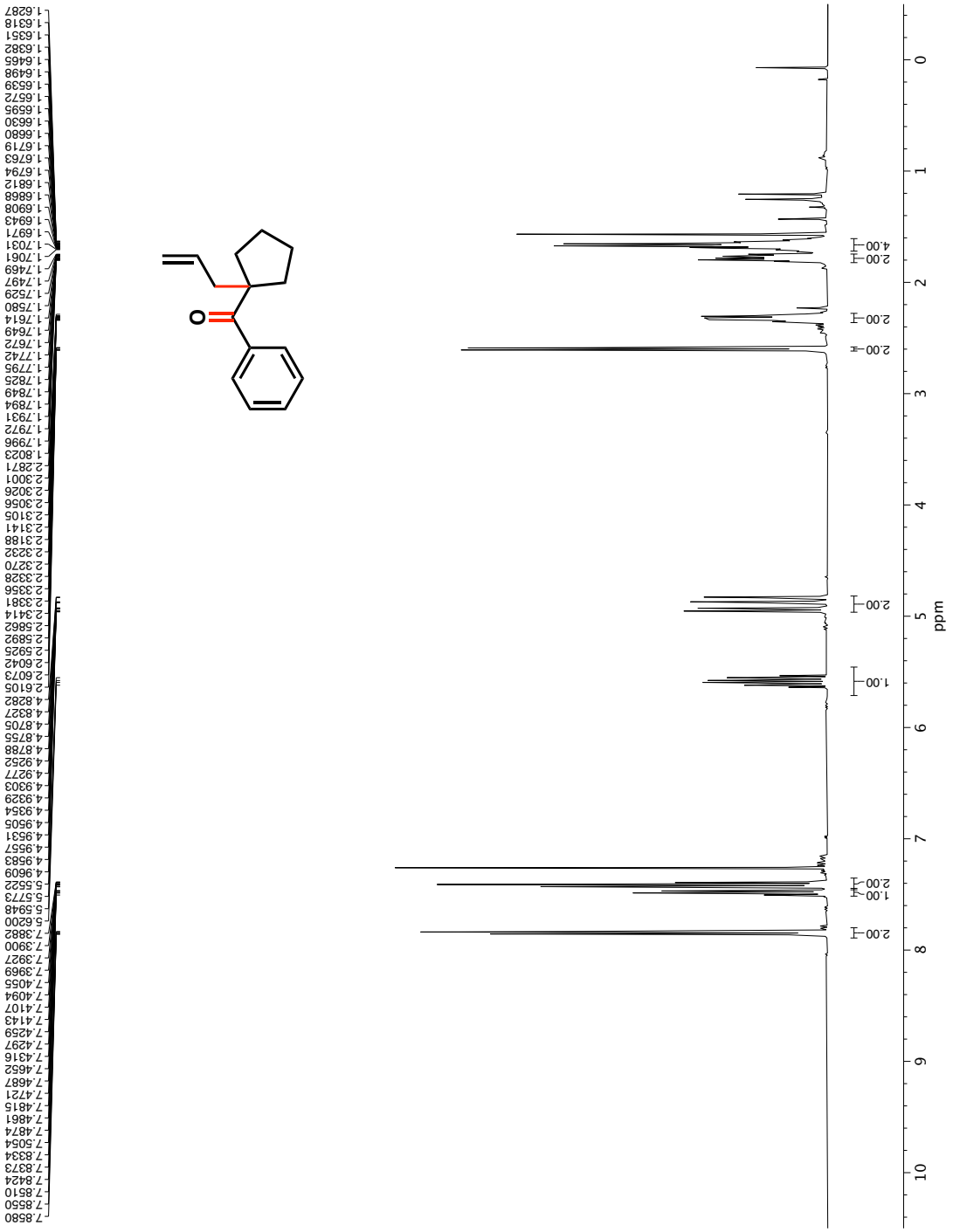
NOESY (400 MHz, $CDCl_3$) of compound **160h**.



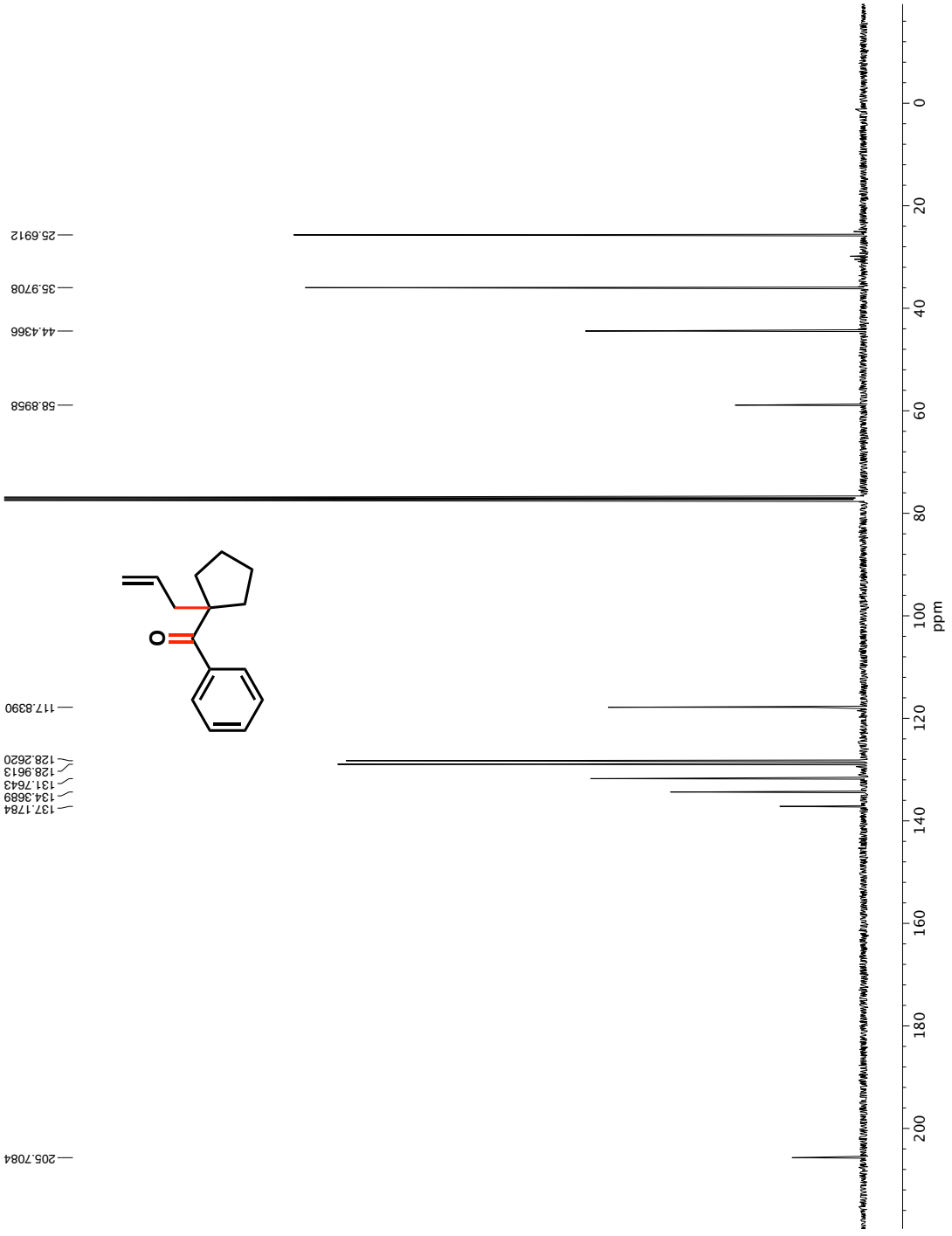
^{1}H NMR (400 MHz, $CDCl_3$) of compound **162**.



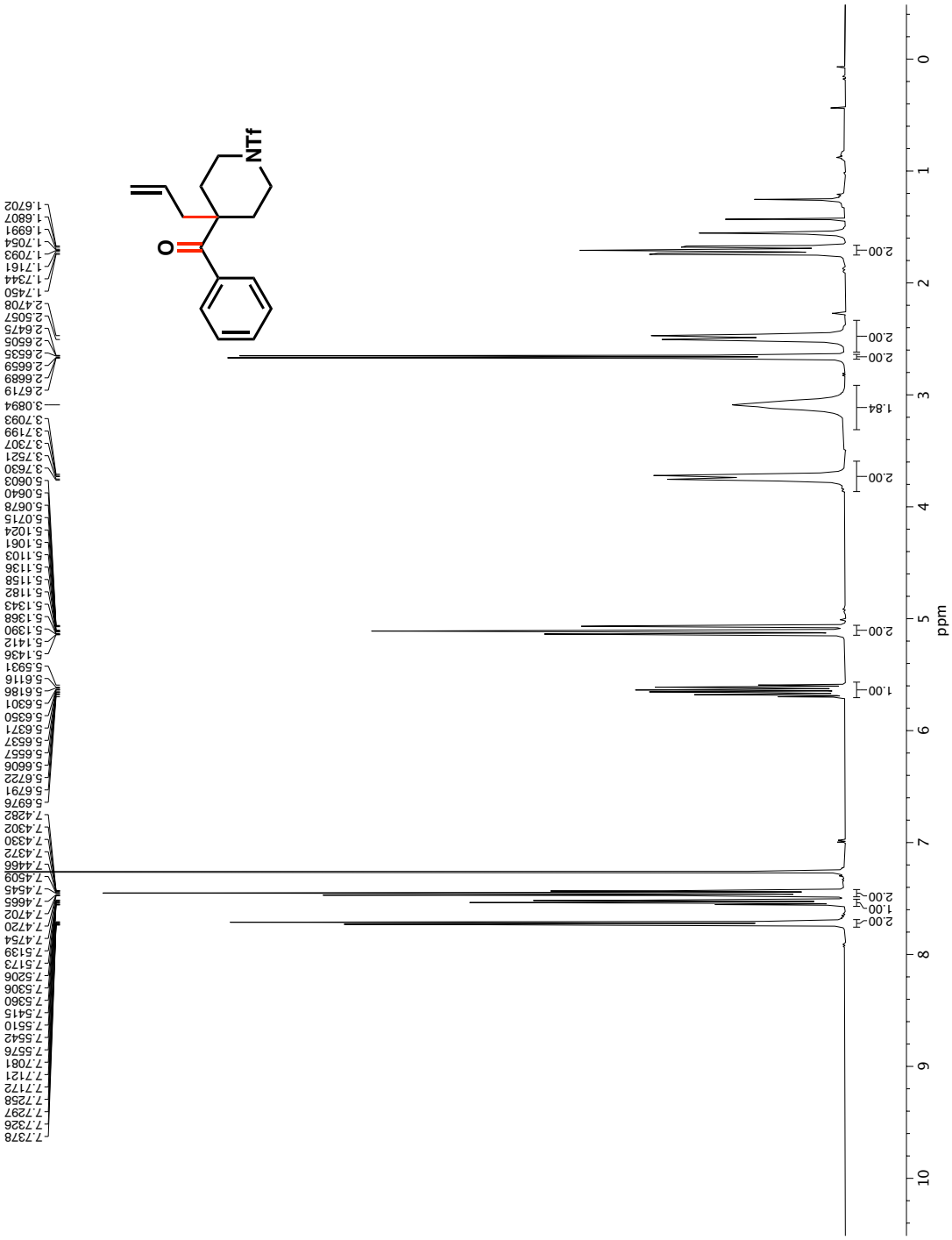
^{13}C NMR (101 MHz, $CDCl_3$) of compound **162**.



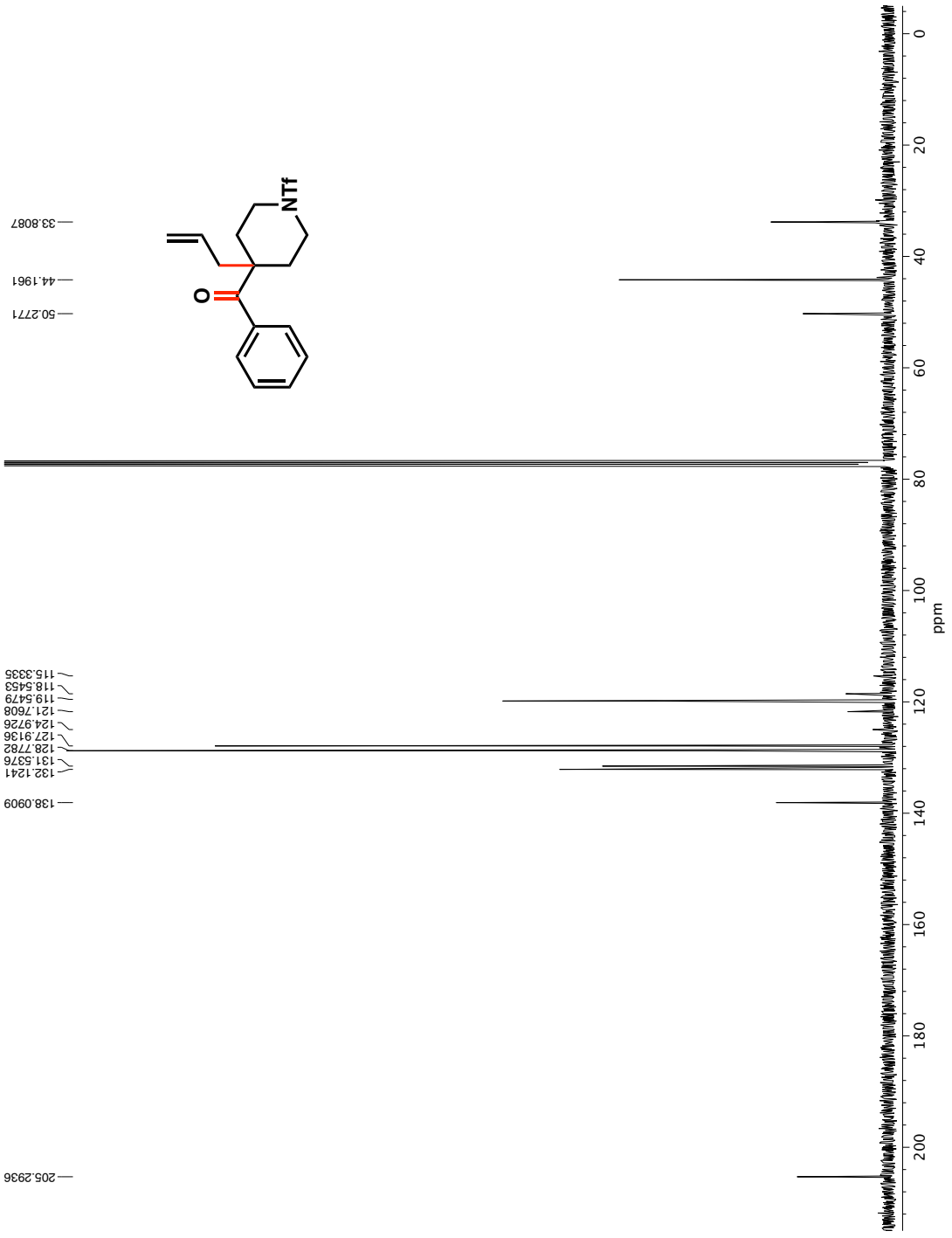
^{1}H NMR (400 MHz, $CDCl_3$) of compound **161b**.



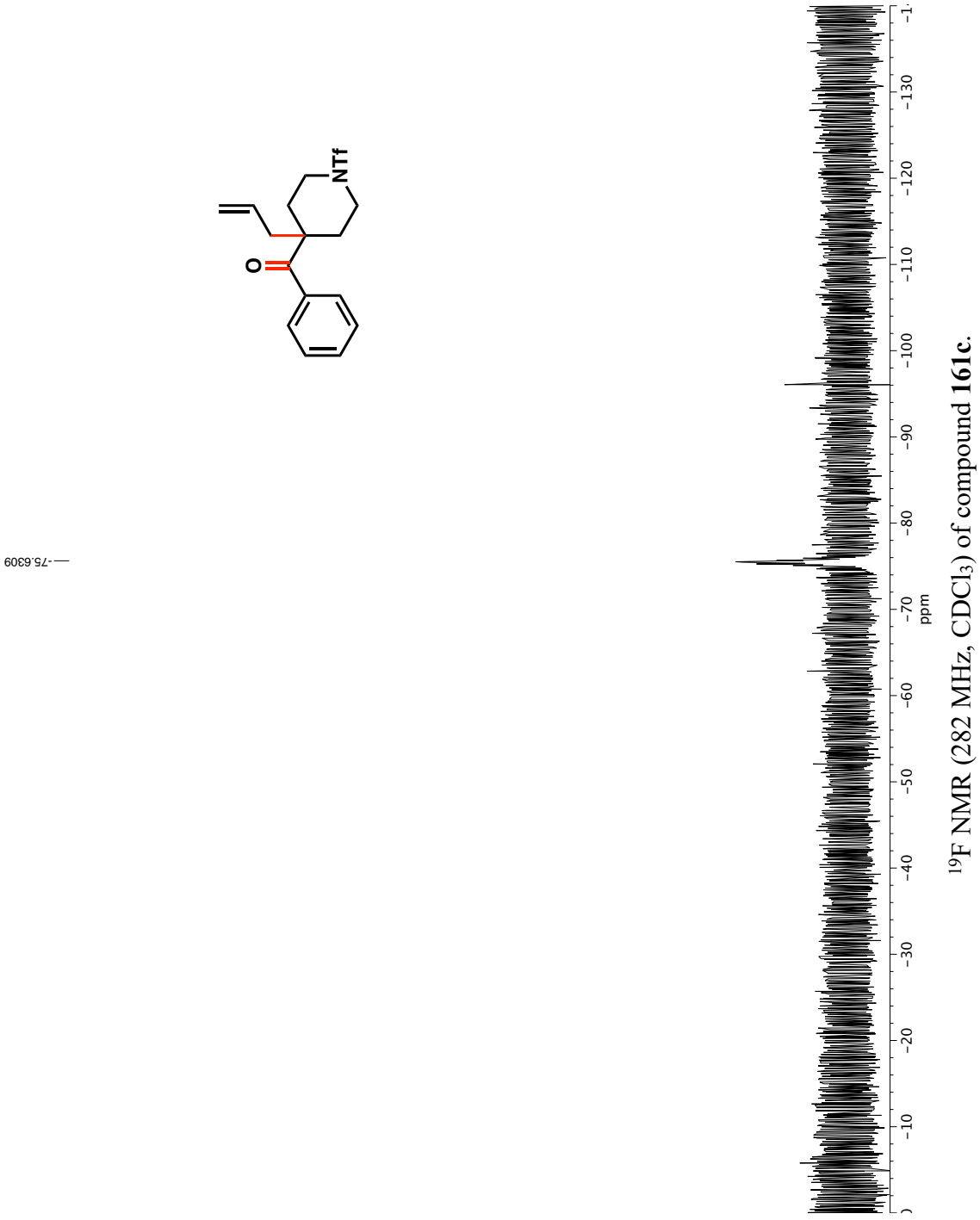
^{13}C NMR (101 MHz, $CDCl_3$) of compound **161b**.



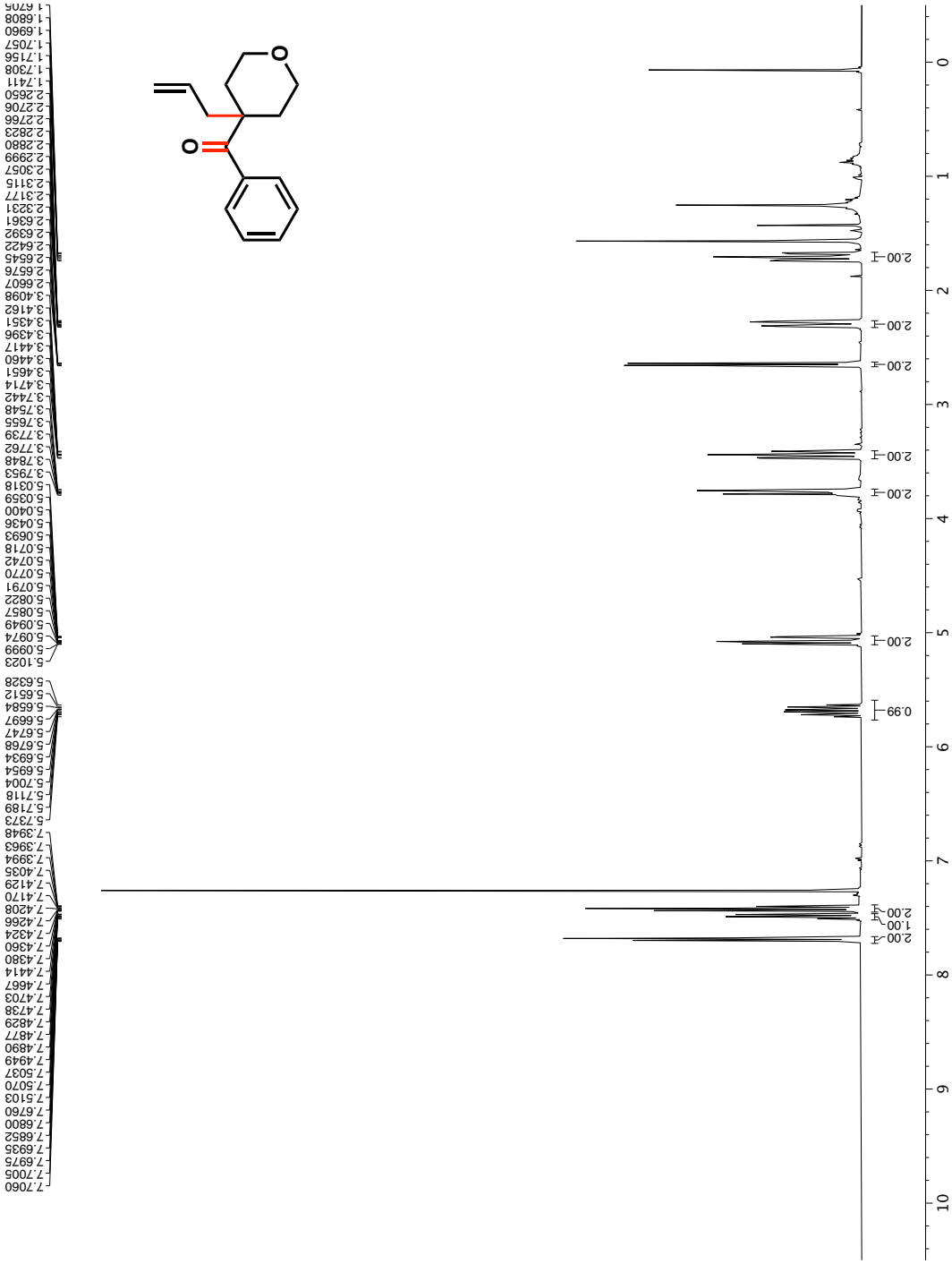
^{1}H NMR (400 MHz, $CDCl_3$) of compound **161c**.



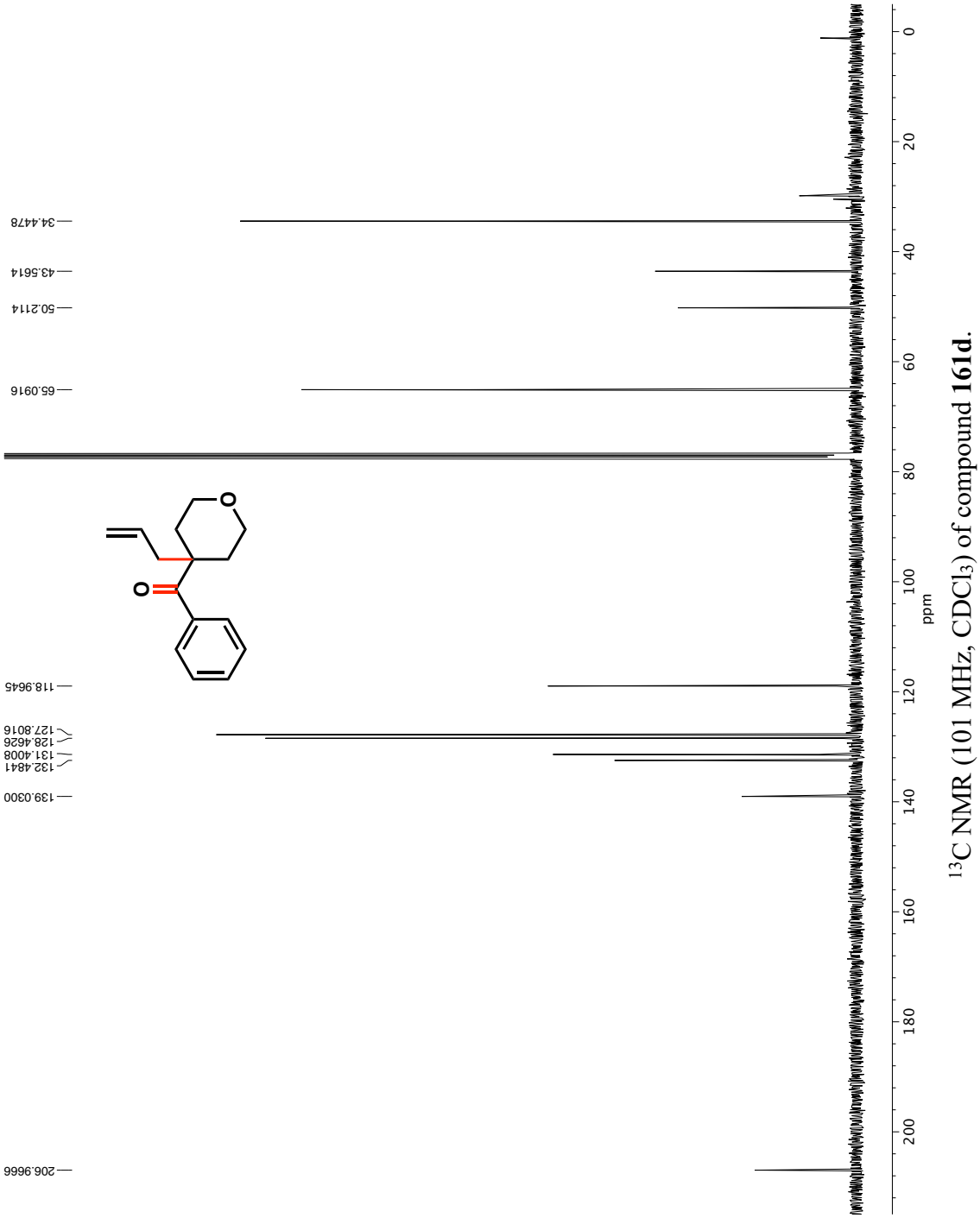
^{13}C NMR (101 MHz, $CDCl_3$) of compound **161c**.



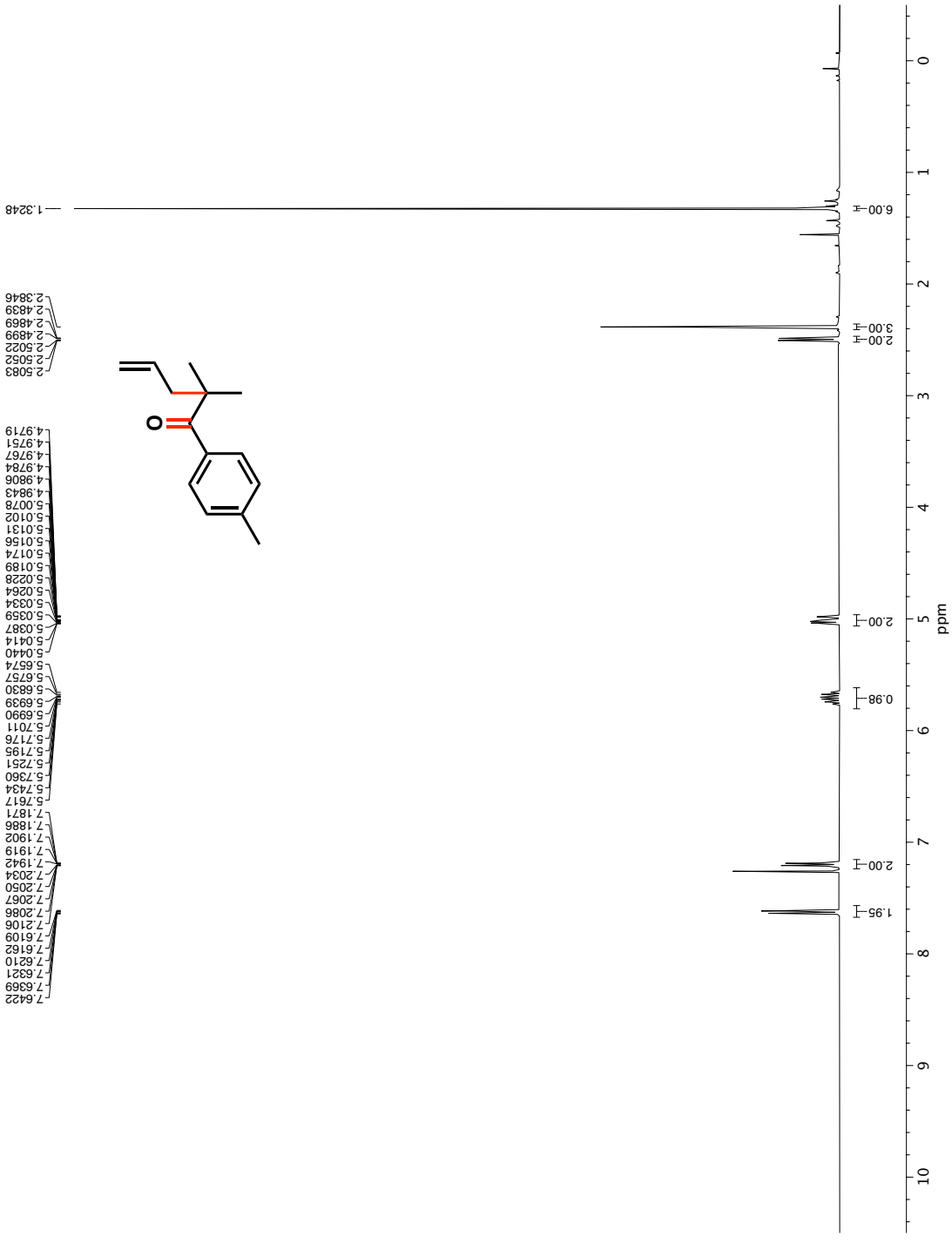
^{19}F NMR (282 MHz, $CDCl_3$) of compound **161c**.



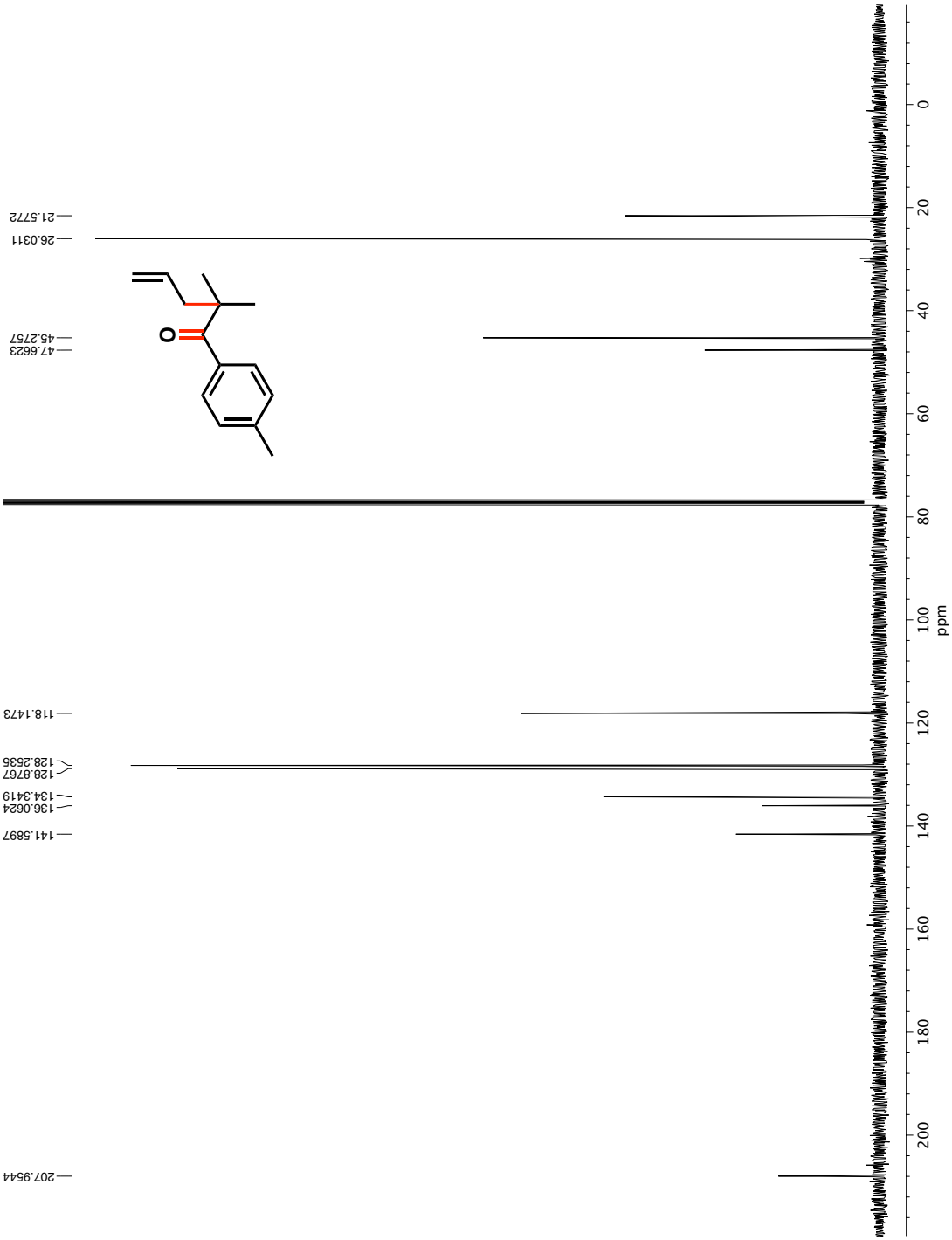
^{1}H NMR (400 MHz, $CDCl_3$) of compound **161d**.



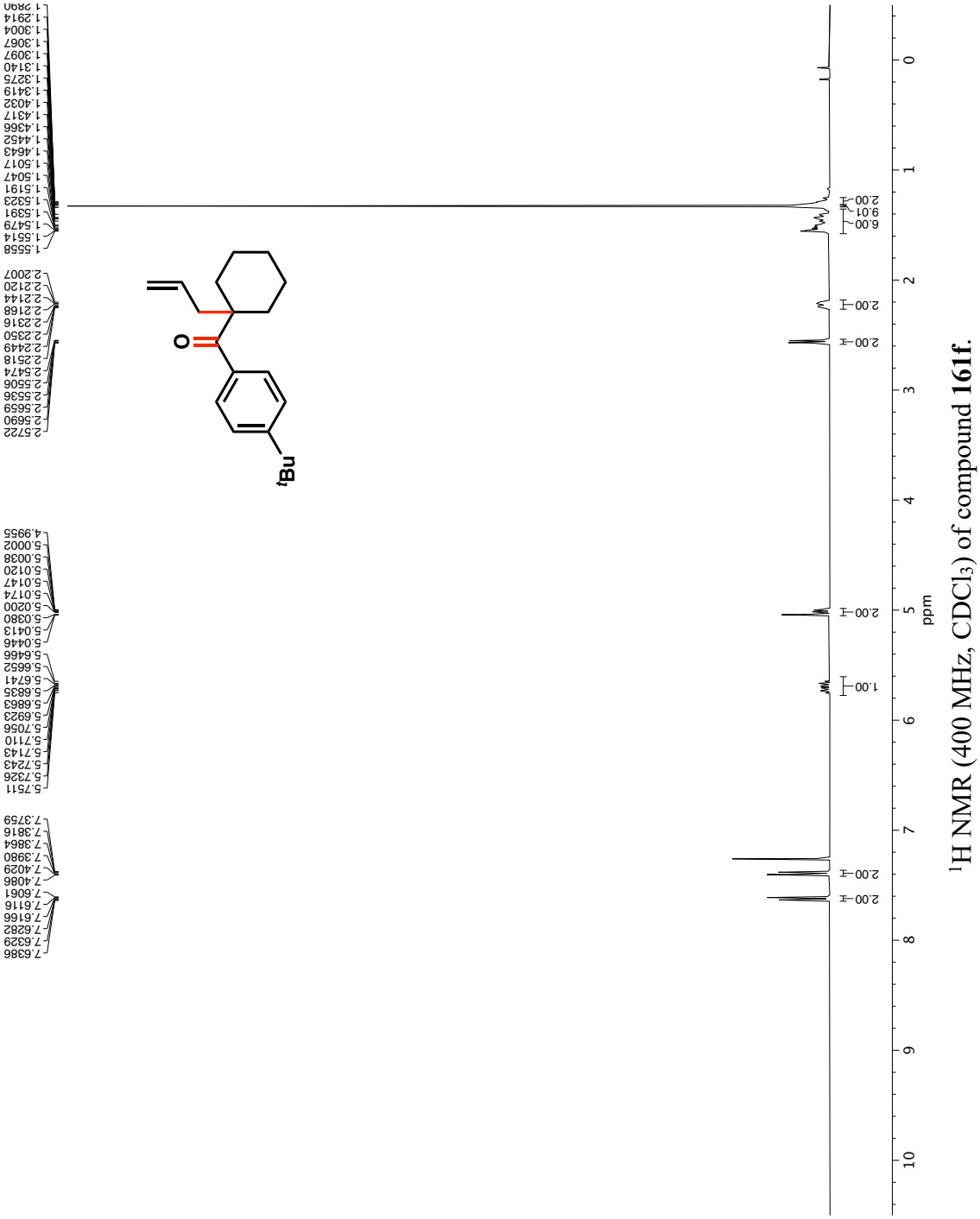
^{13}C NMR (101 MHz, $CDCl_3$) of compound **161d**.



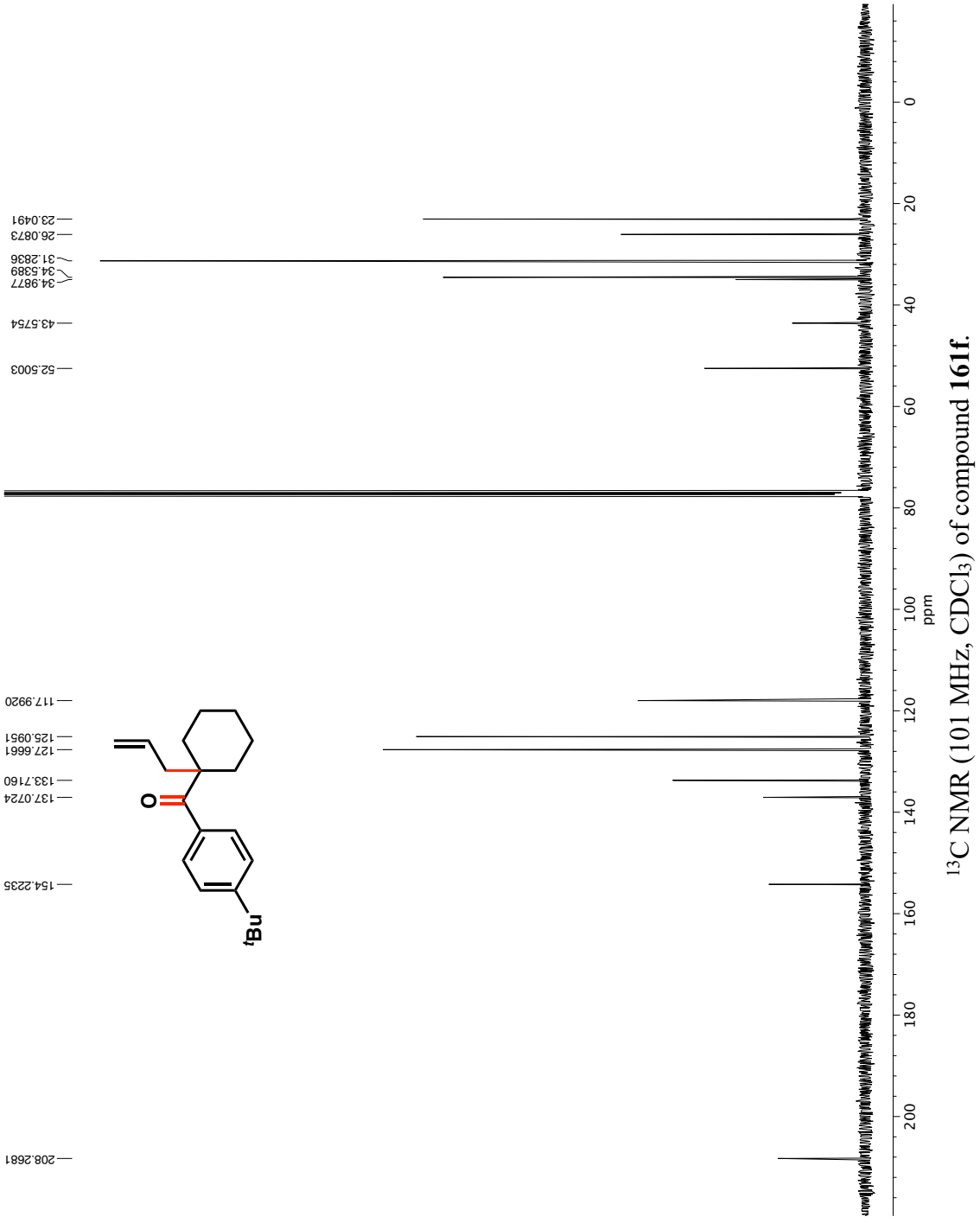
^{1}H NMR (400 MHz, $CDCl_3$) of compound **161e**.



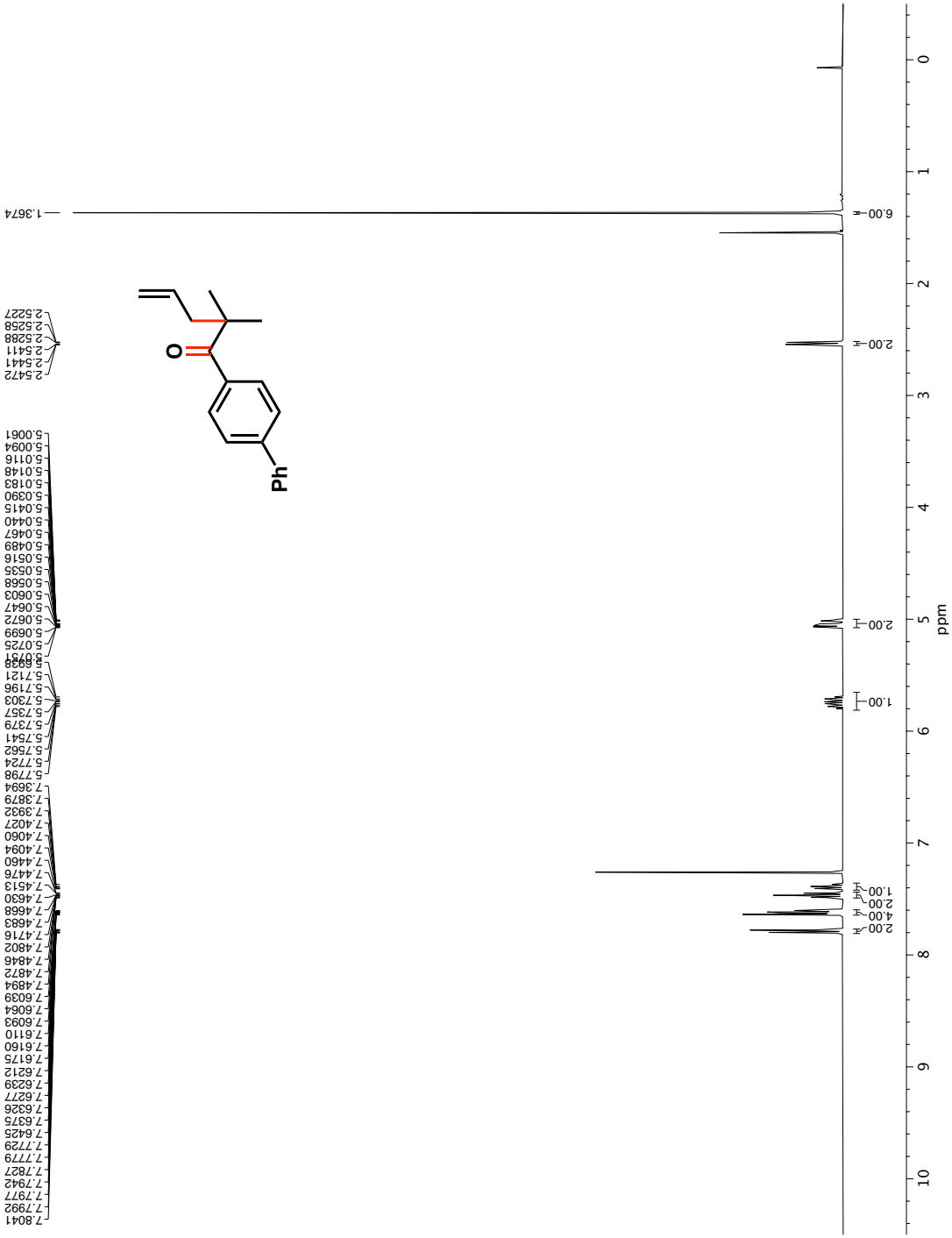
^{13}C NMR (101 MHz, $CDCl_3$) of compound **161e**.



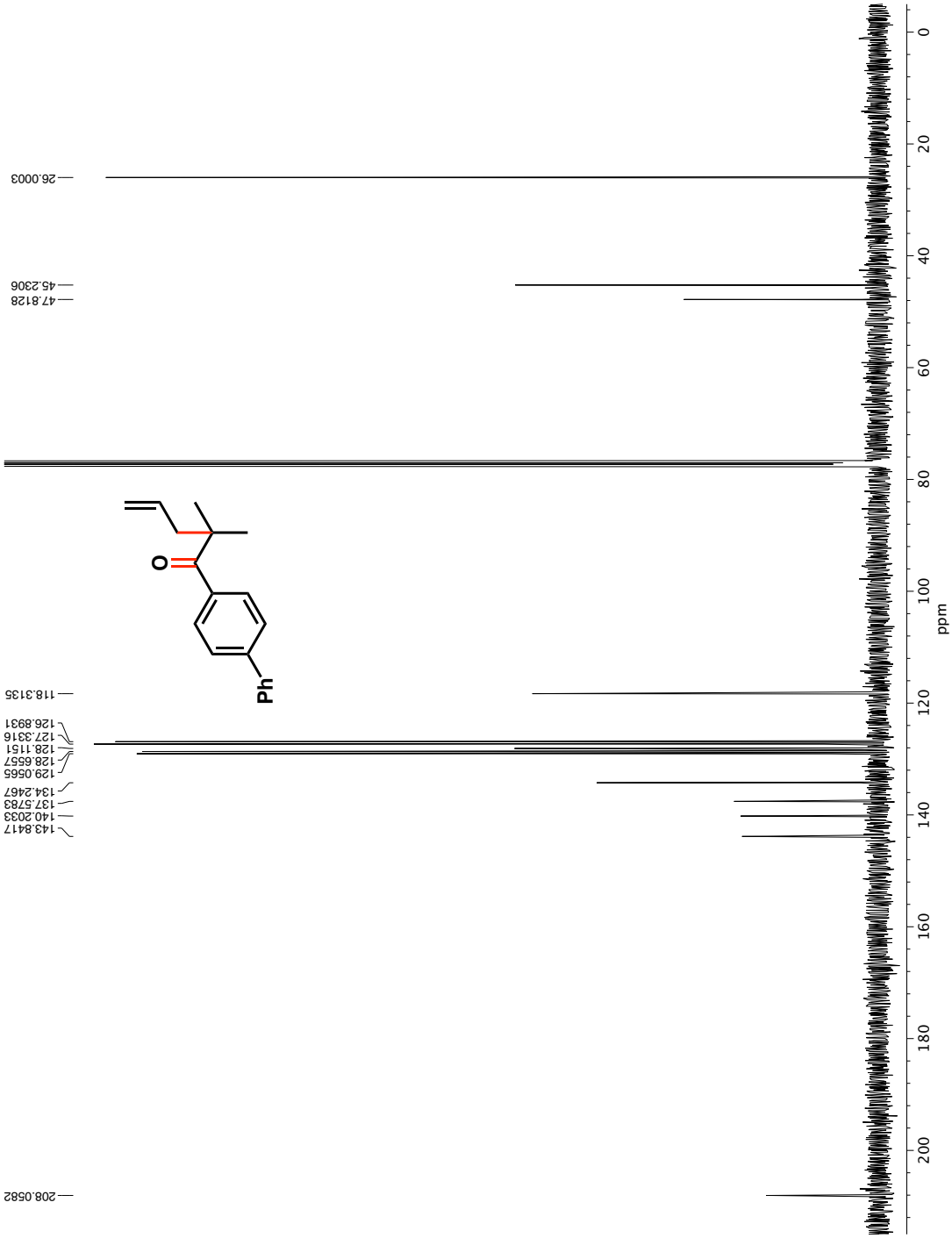
^{1}H NMR (400 MHz, $CDCl_3$) of compound **161f**.



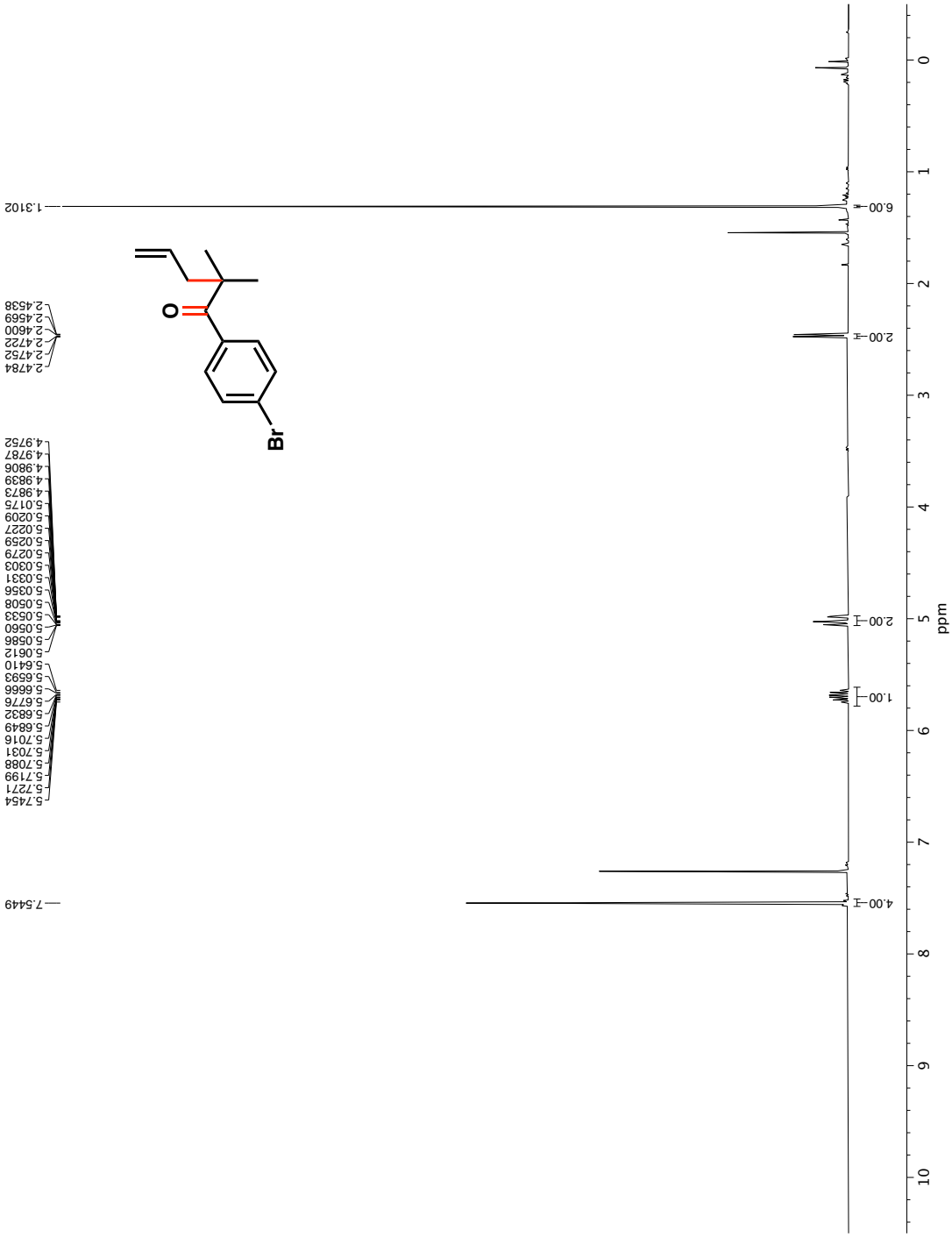
^{13}C NMR (101 MHz, $CDCl_3$) of compound **161f**.



^{1}H NMR (400 MHz, $CDCl_3$) of compound **161g**.

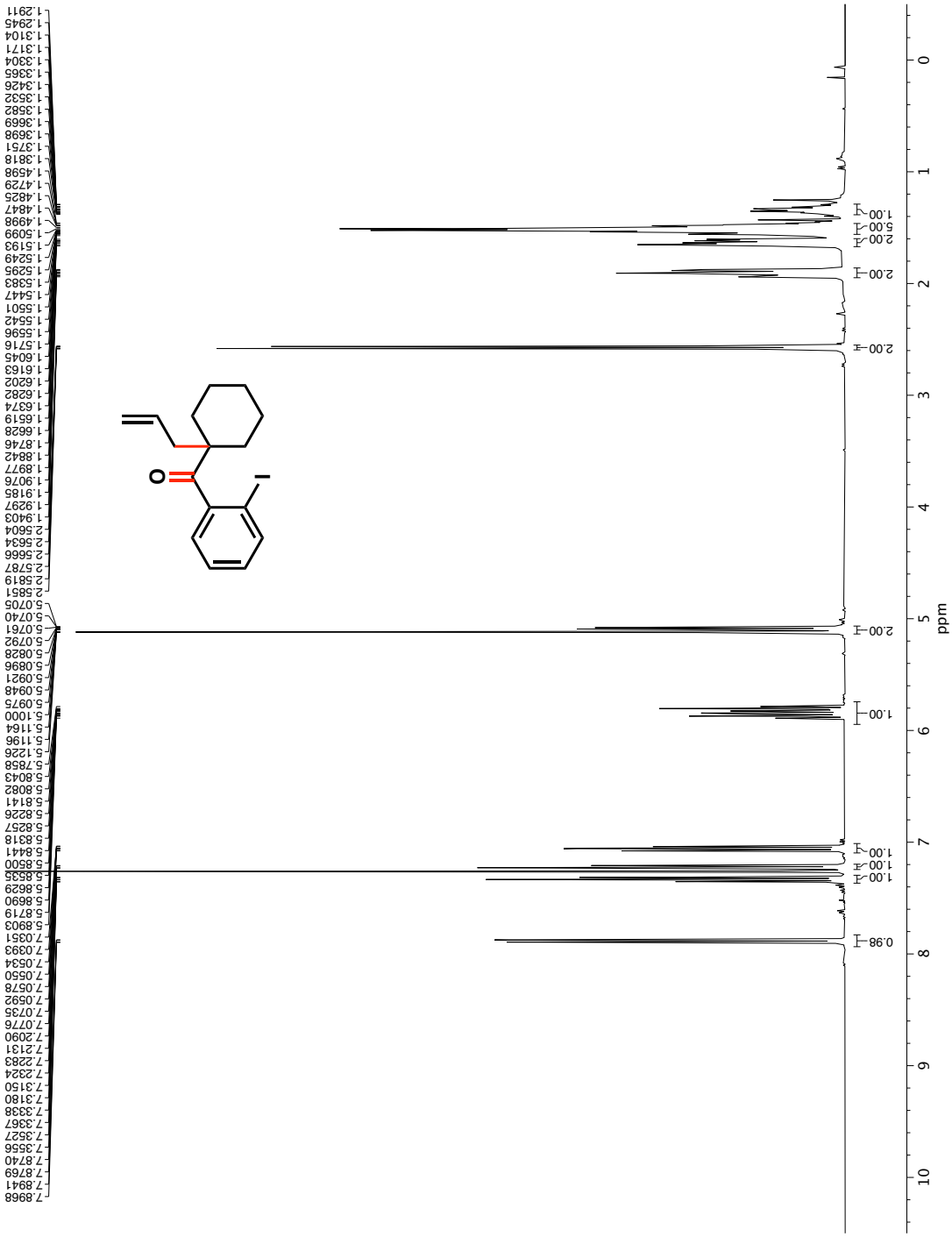


^{13}C NMR (101 MHz, $CDCl_3$) of compound **161g.**

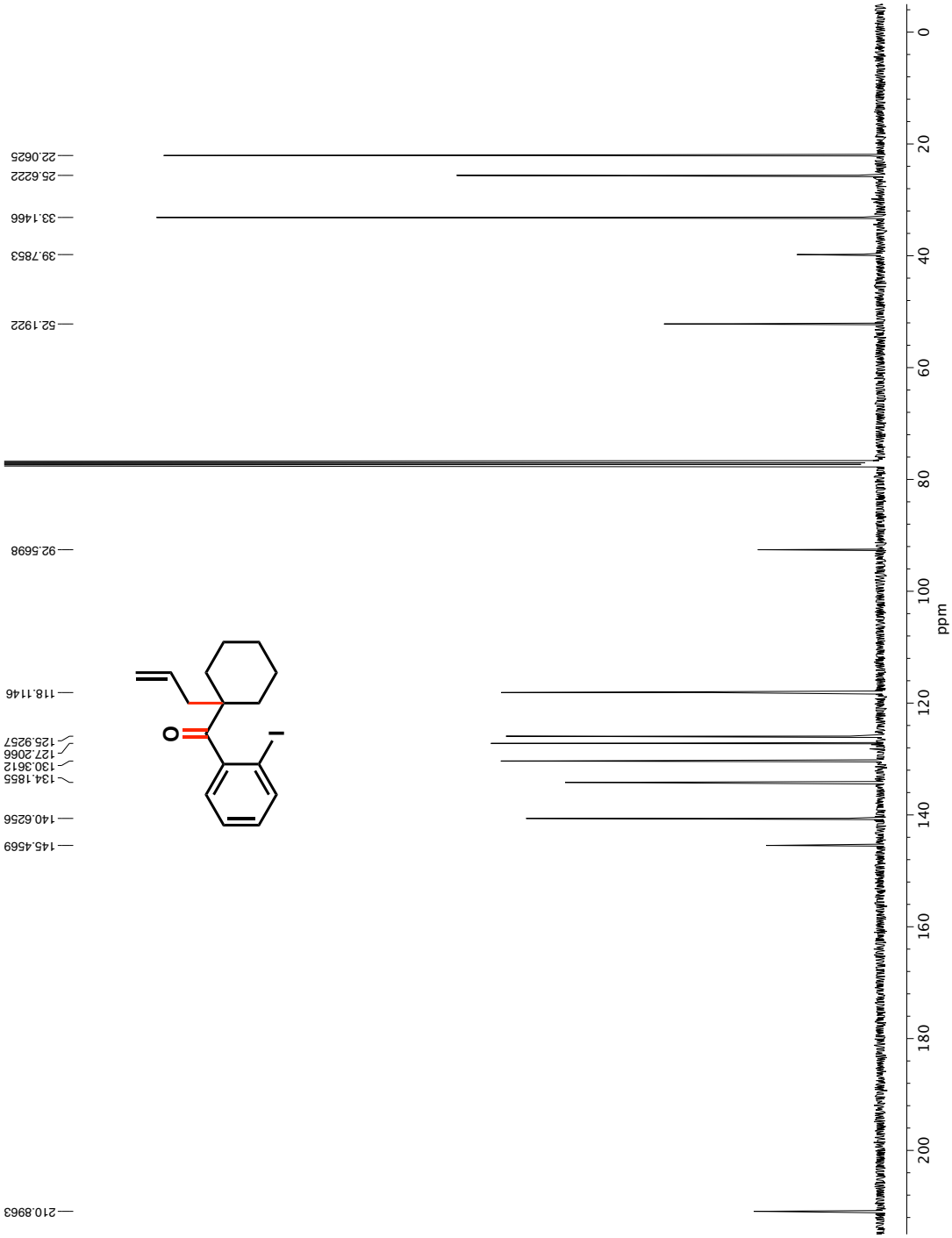


^{1}H NMR (400 MHz, $CDCl_3$) of compound **161h**.

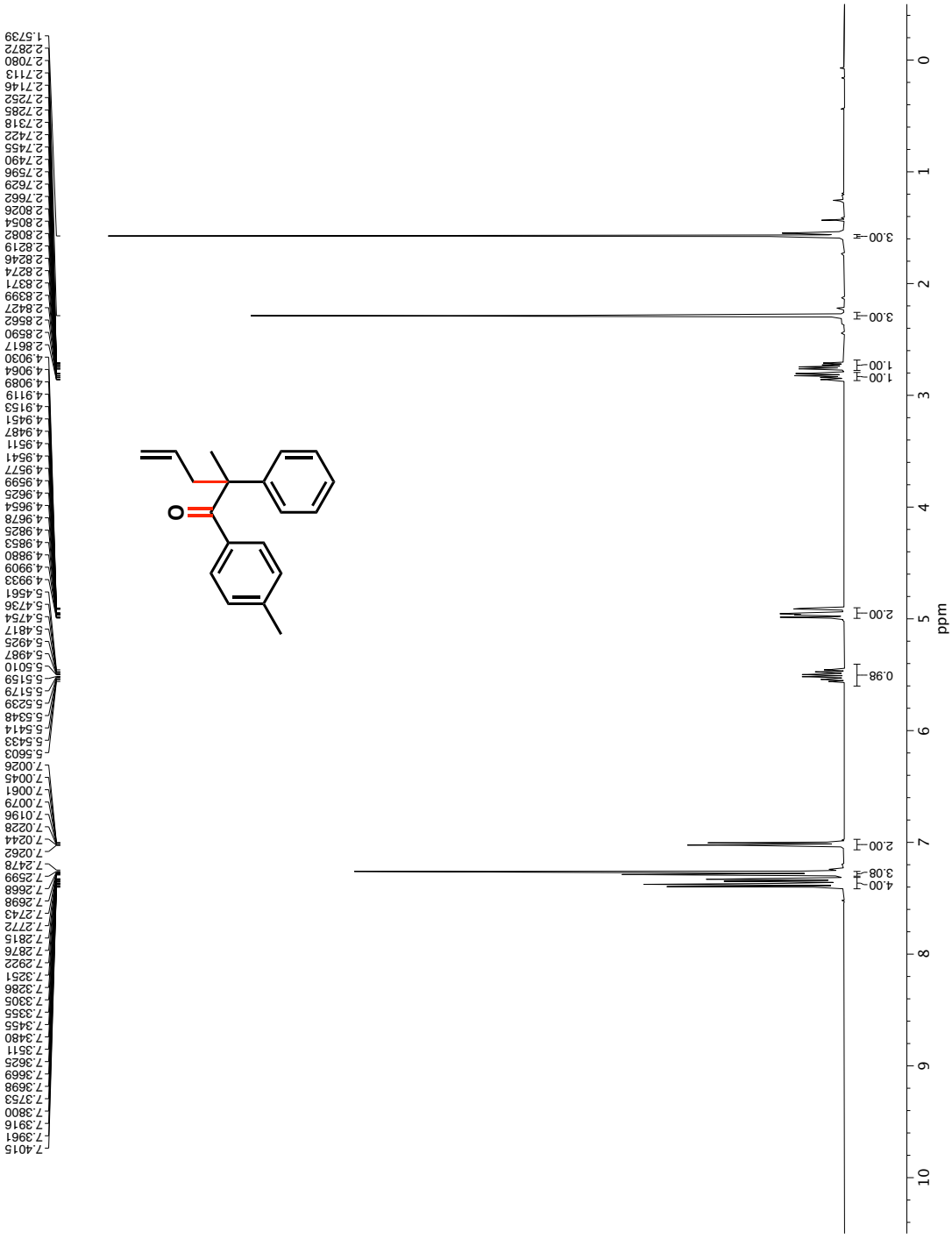
^{13}C NMR (101 MHz, $CDCl_3$) of compound **161h**.



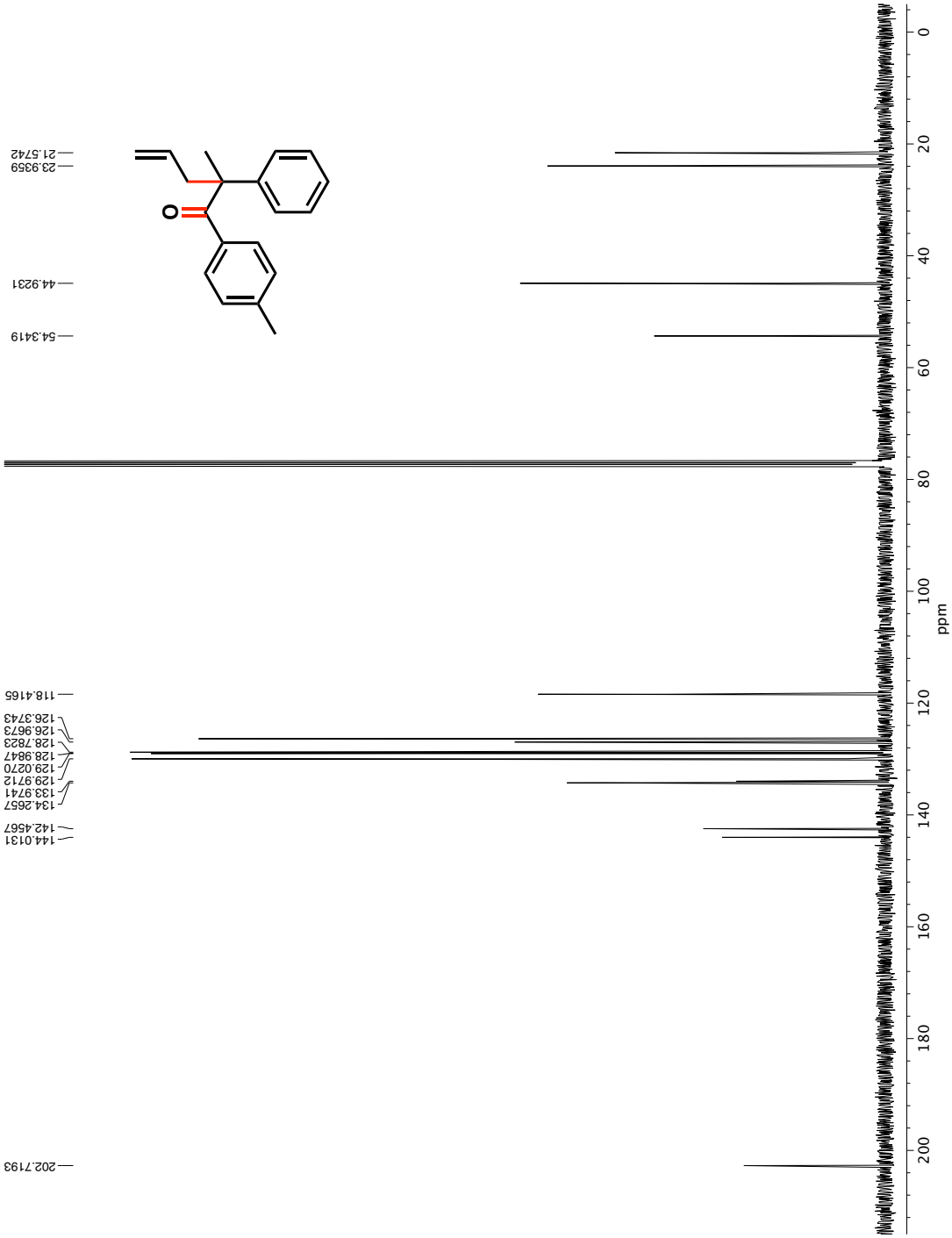
^{1}H NMR (400 MHz, $CDCl_3$) of compound **161i**.



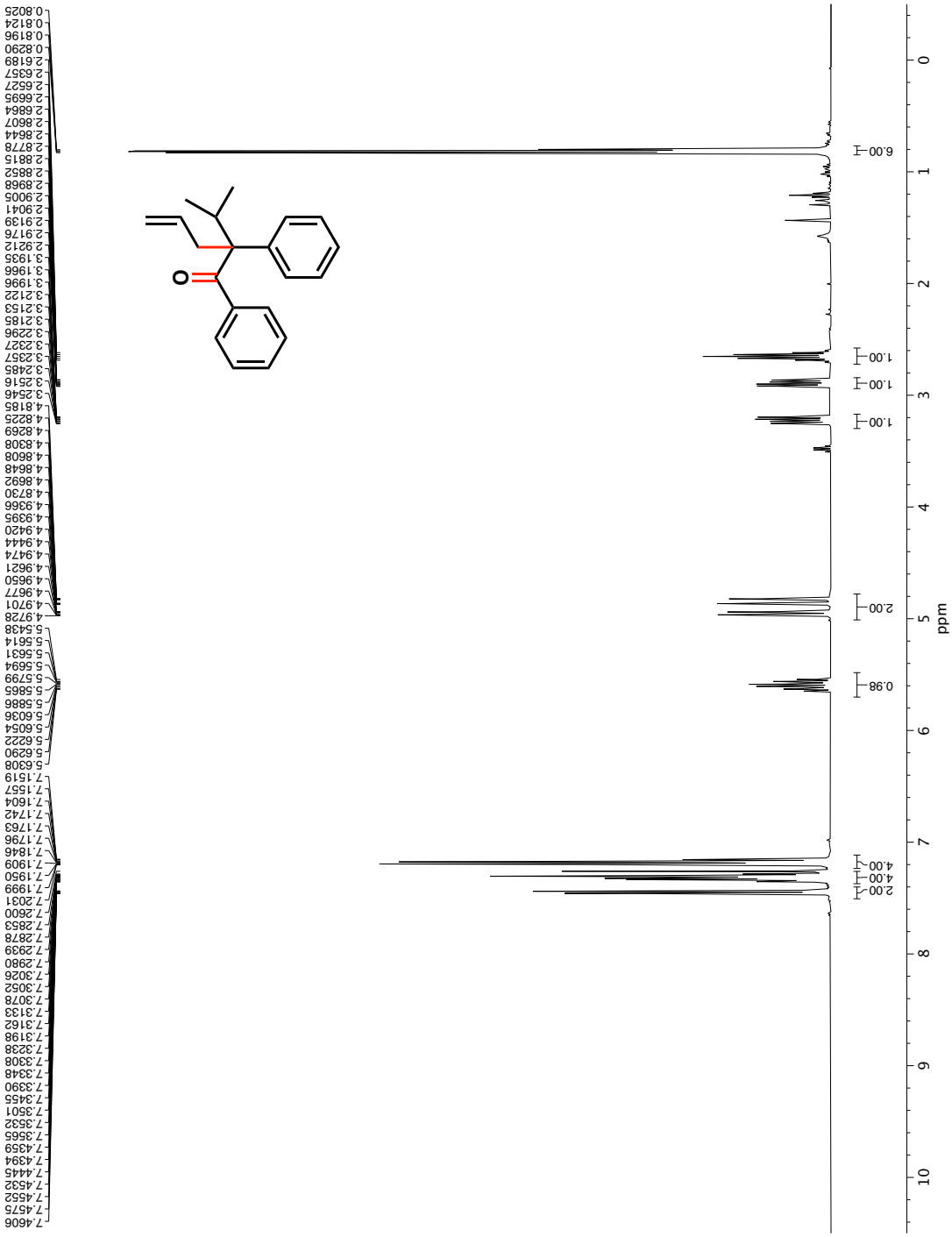
^{13}C NMR (101 MHz, $CDCl_3$) of compound **161i**.



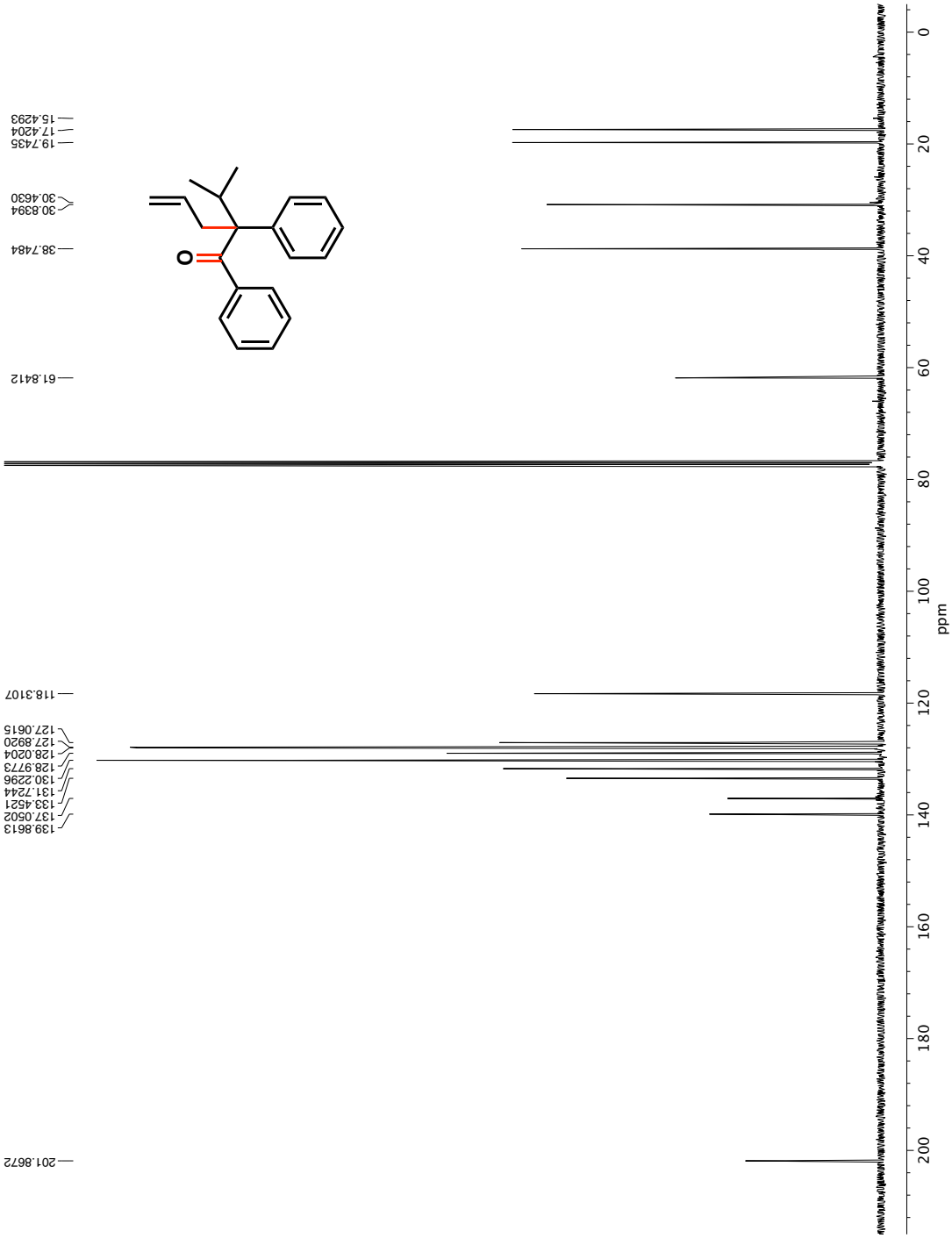
^{1}H NMR (400 MHz, $CDCl_3$) of compound **161k**.



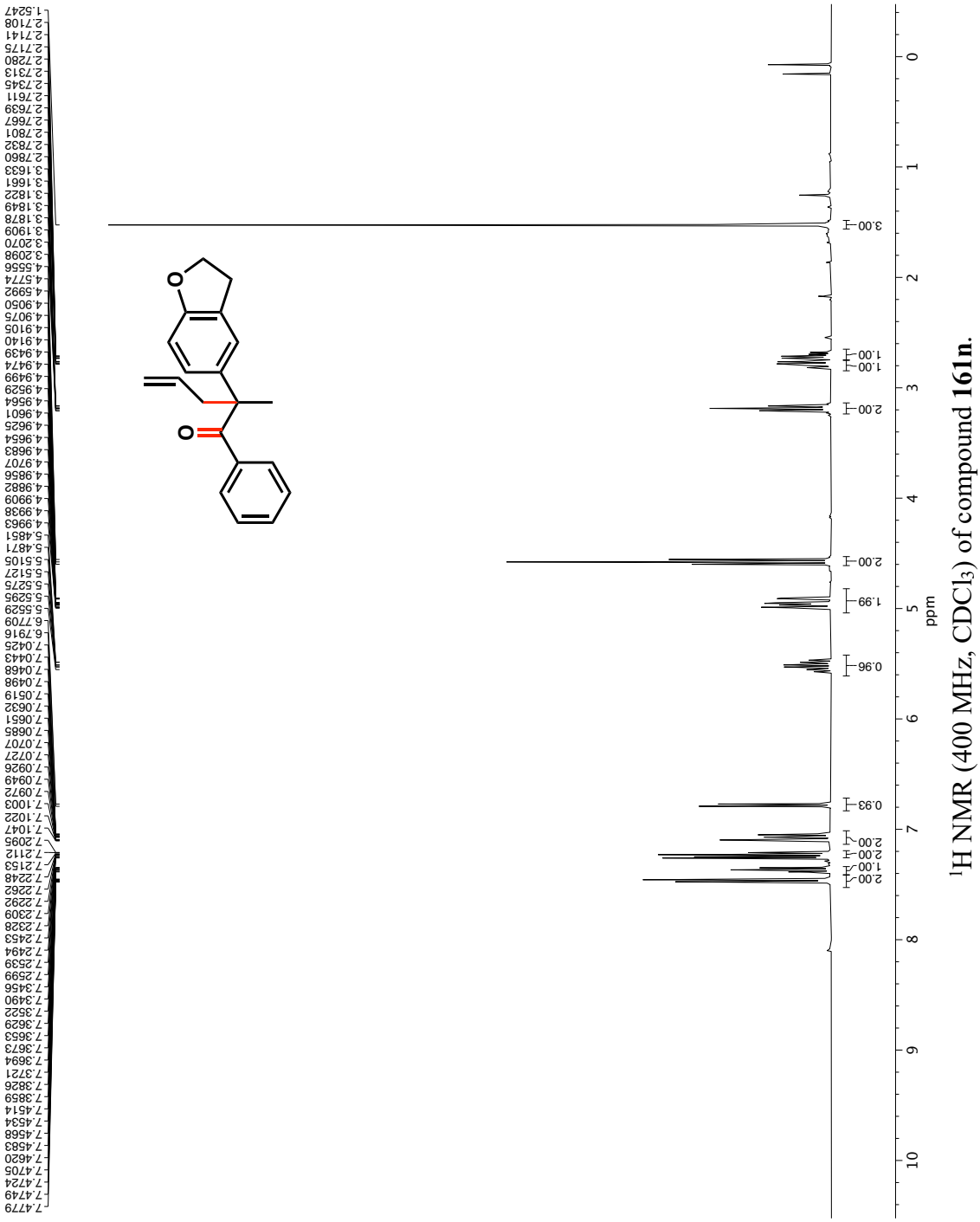
^{13}C NMR (101 MHz, $CDCl_3$) of compound **161k**.



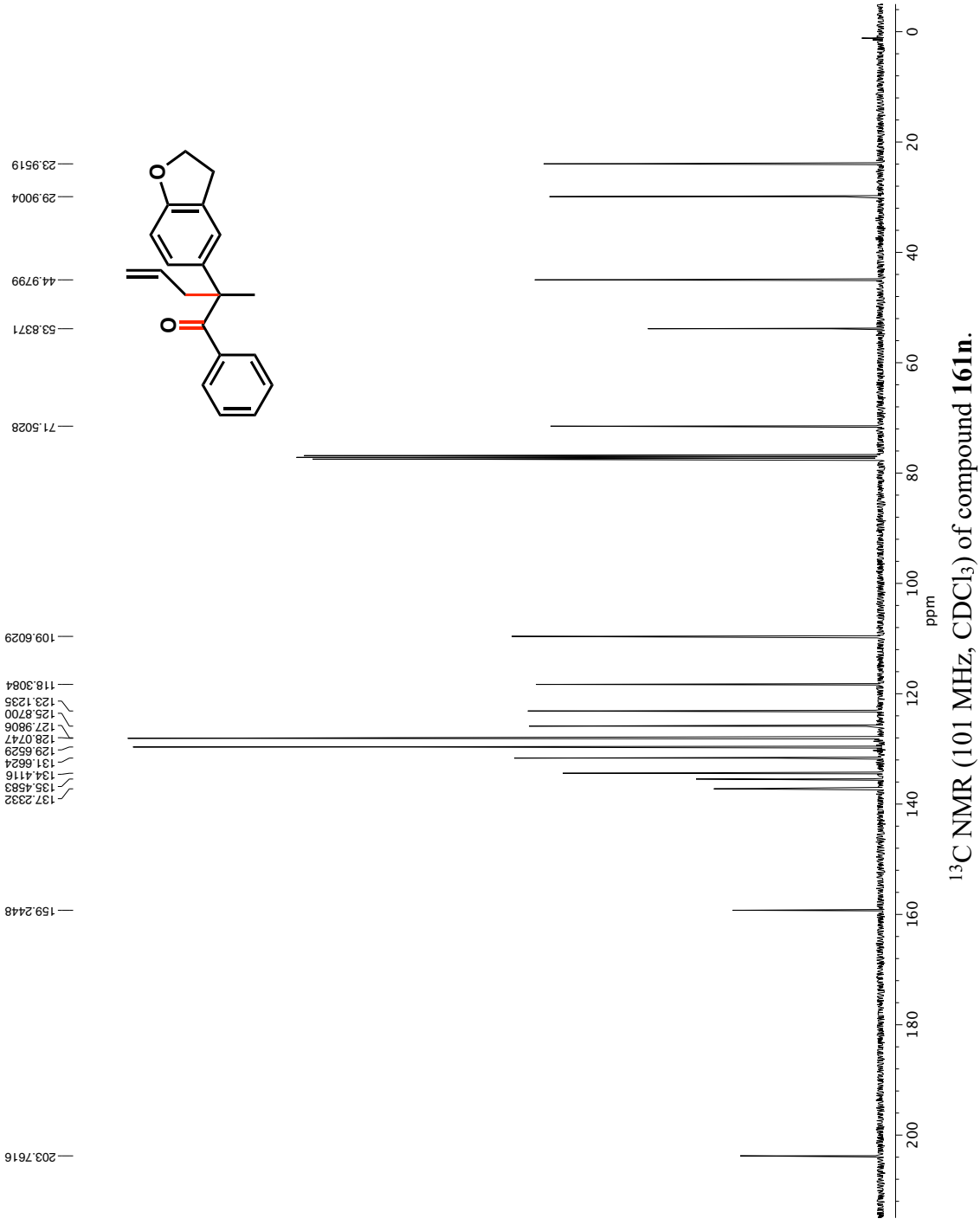
^{1}H NMR (400 MHz, $CDCl_3$) of compound **1611**.



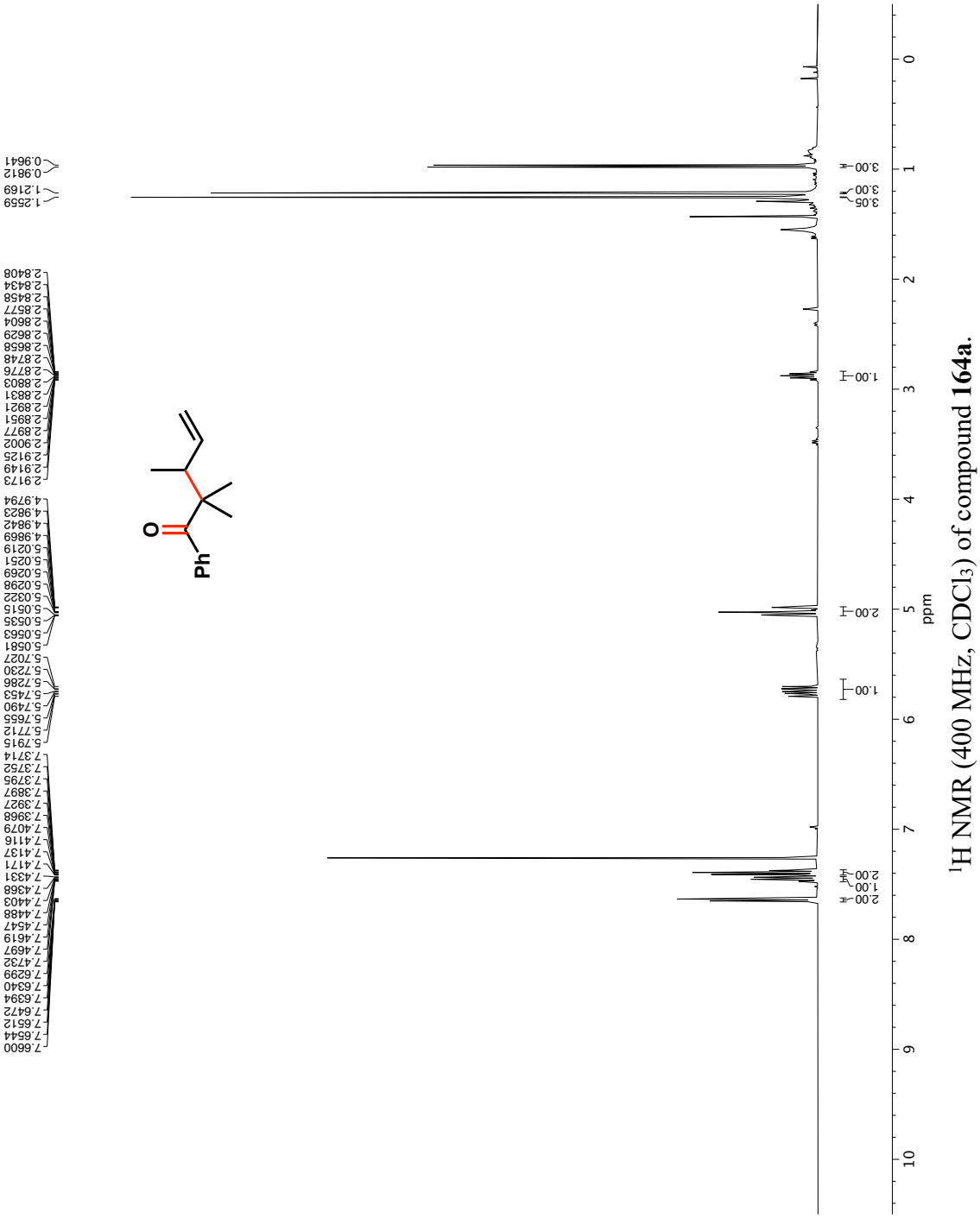
^{13}C NMR (101 MHz, $CDCl_3$) of compound **161l**.



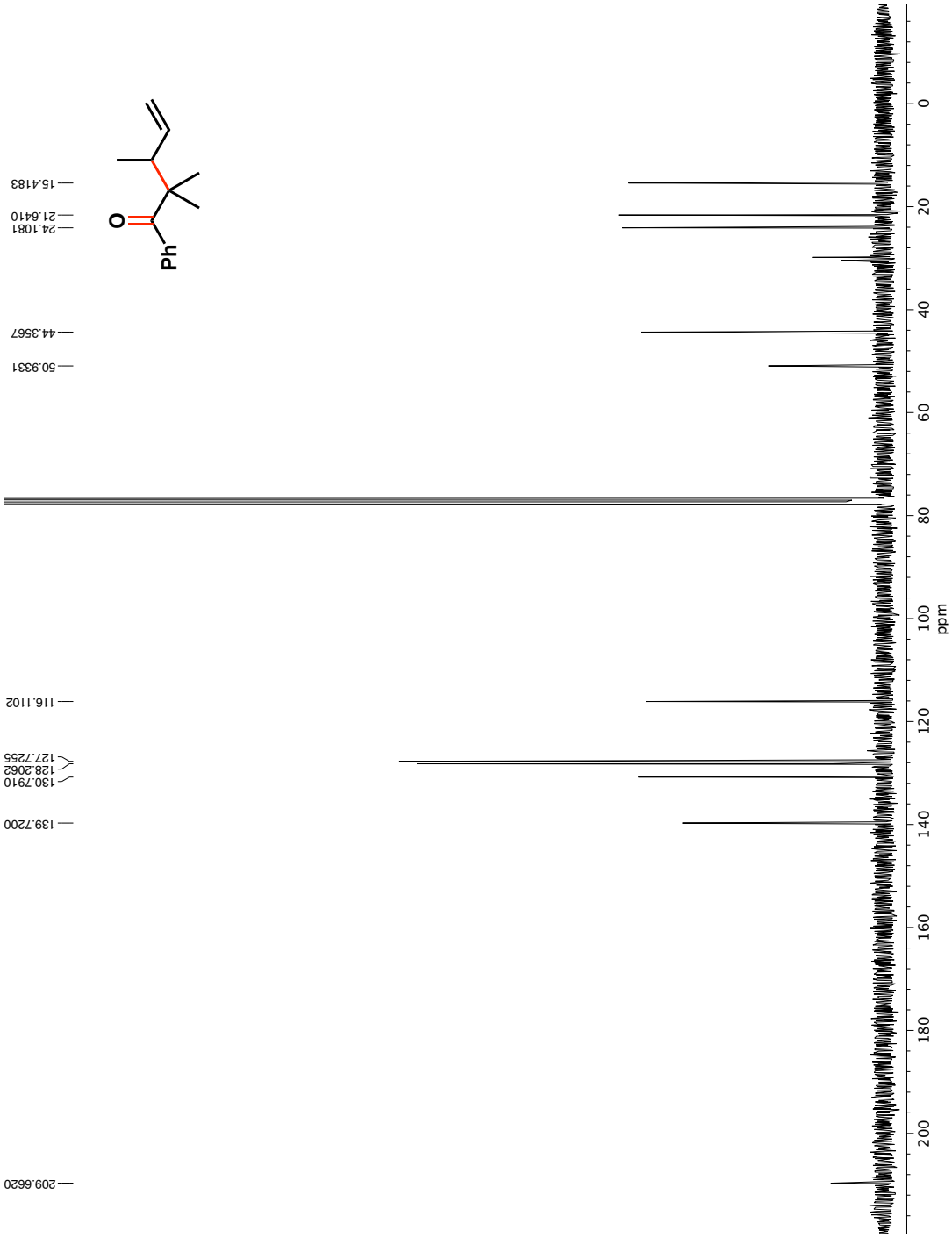
^{1}H NMR (400 MHz, $CDCl_3$) of compound **161n**.



^{13}C NMR (101 MHz, $CDCl_3$) of compound **161n**.

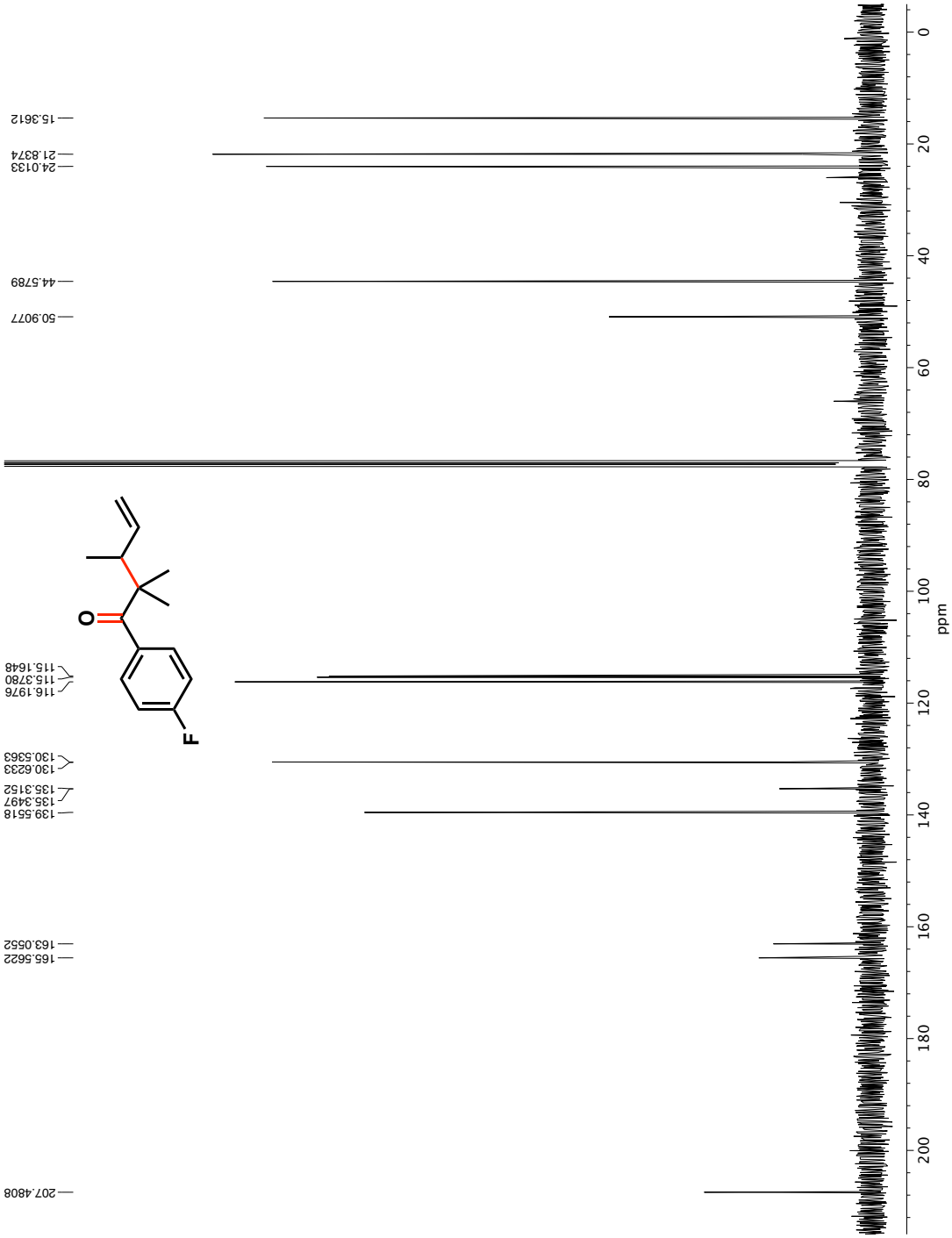


^{1}H NMR (400 MHz, $CDCl_3$) of compound **164a**.

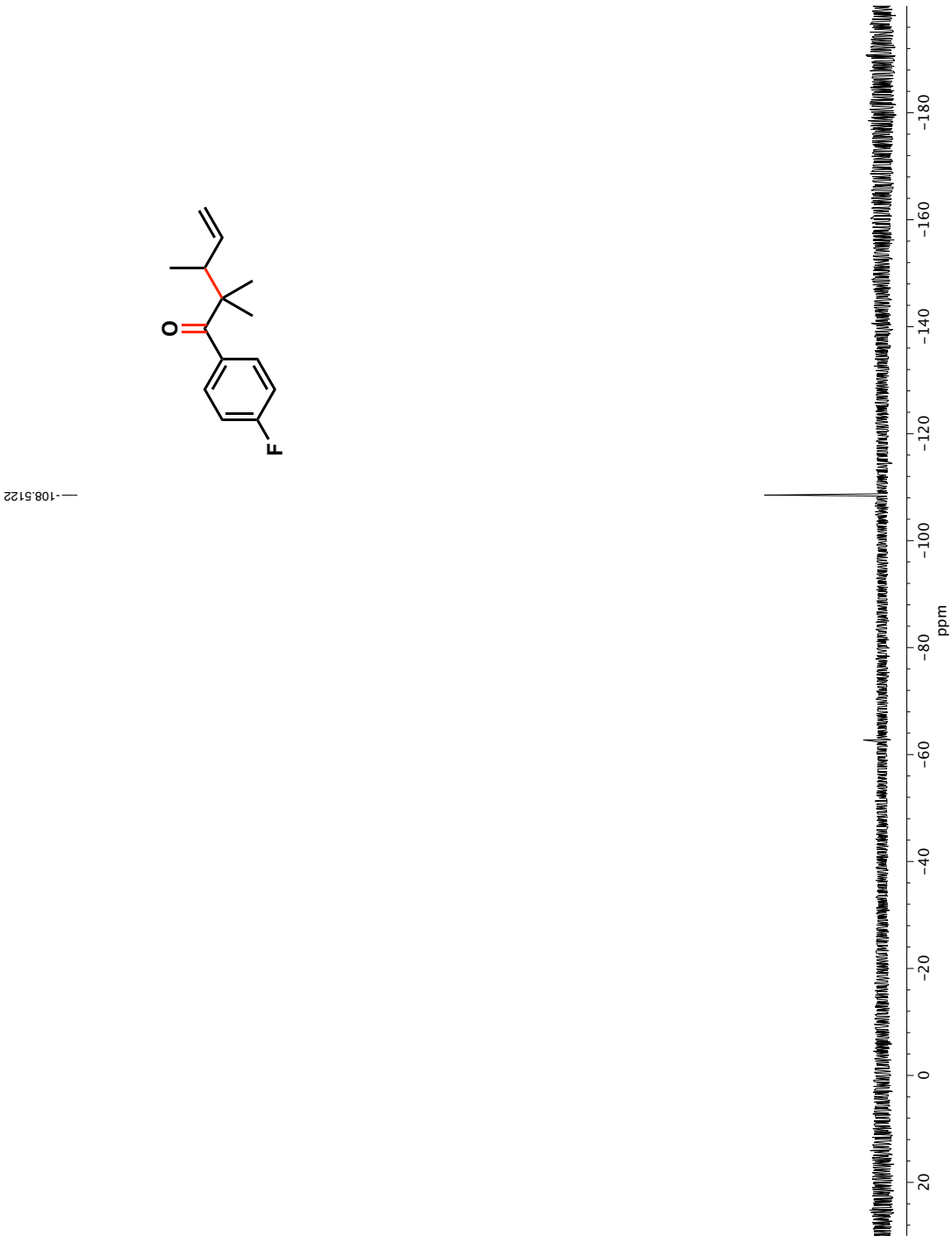


^{13}C NMR (101 MHz, $CDCl_3$) of compound **164a**.

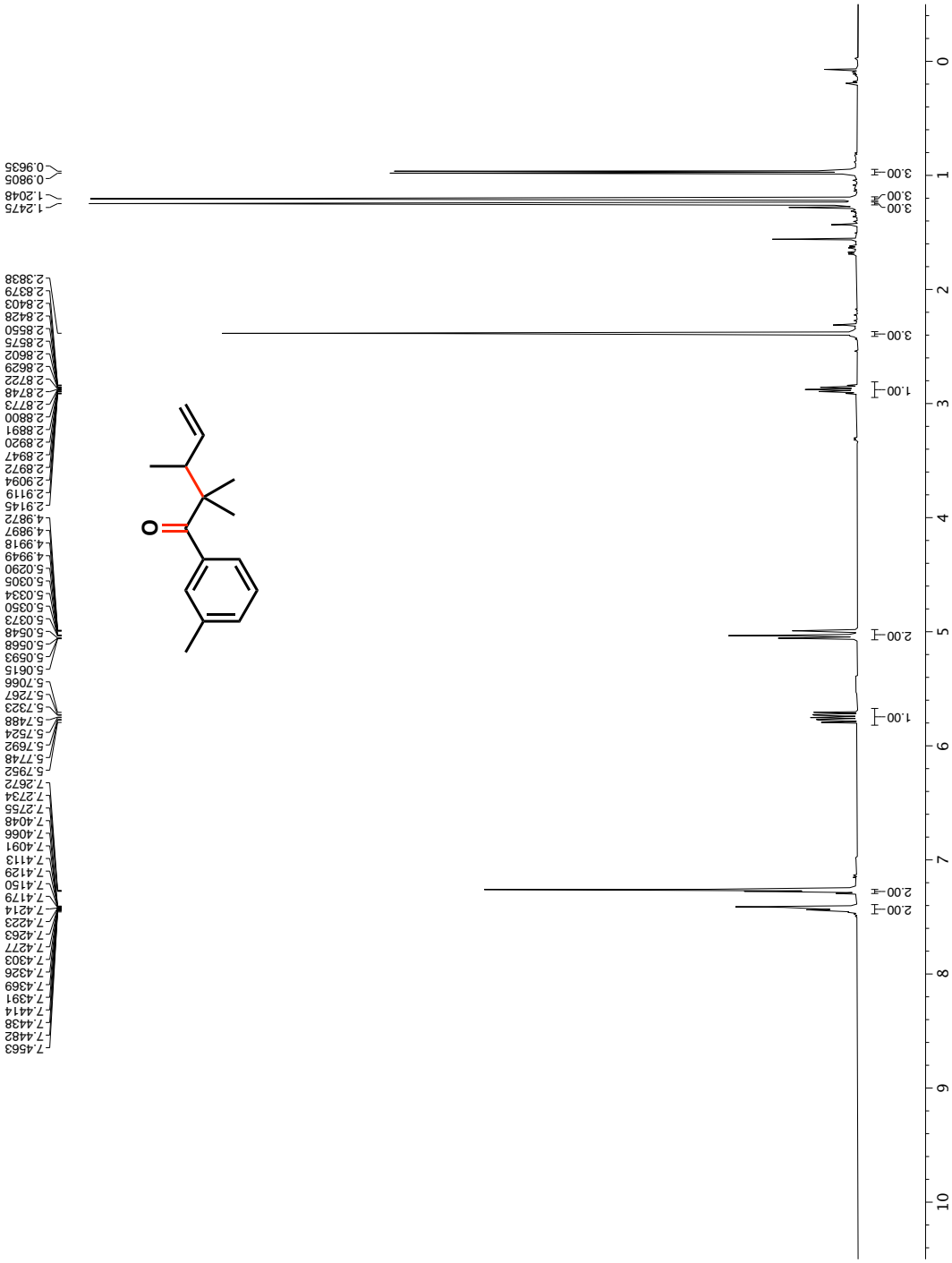
^{1}H NMR (400 MHz, $CDCl_3$) of compound **164b**.



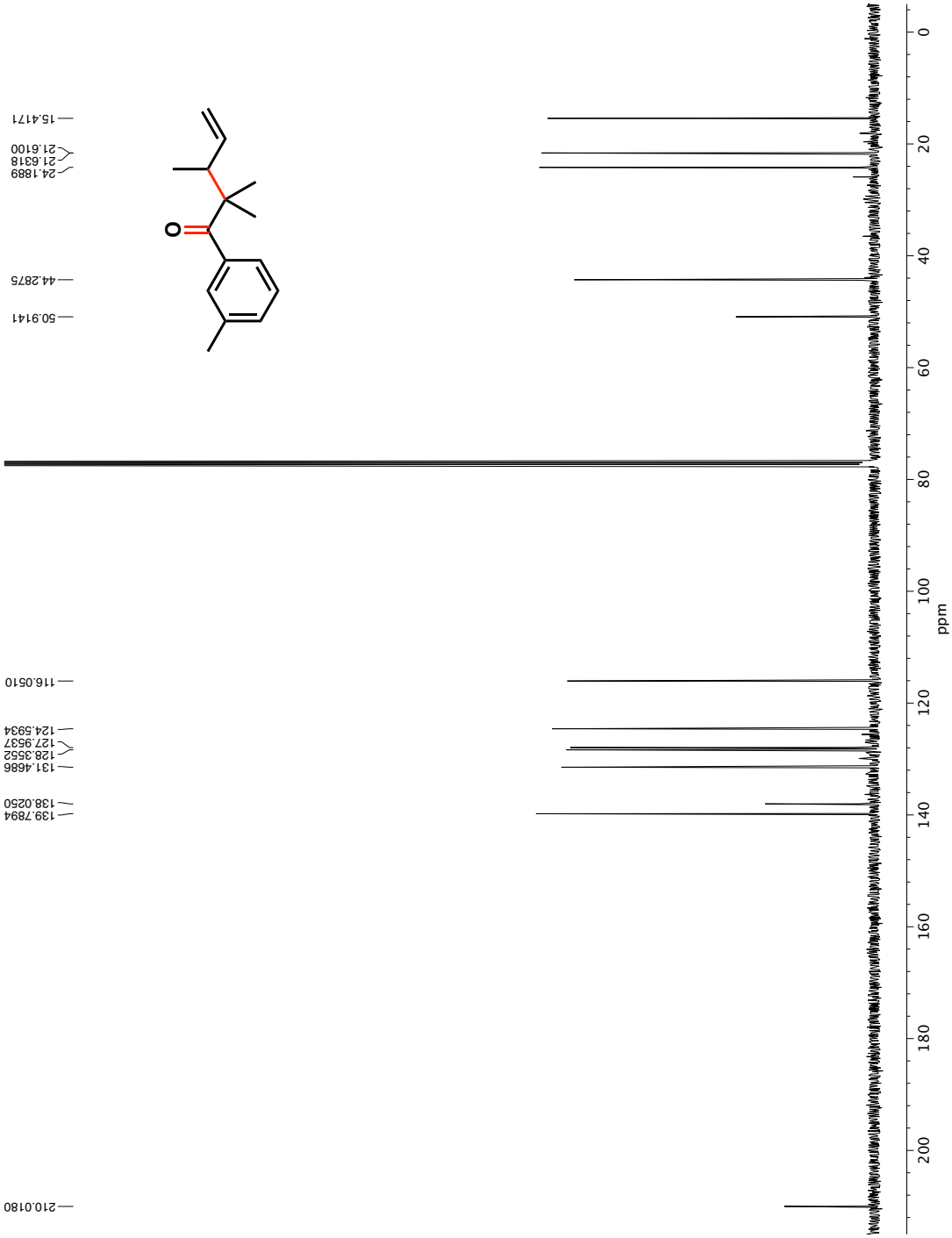
^{13}C NMR (101 MHz, $CDCl_3$) of compound **164b**.



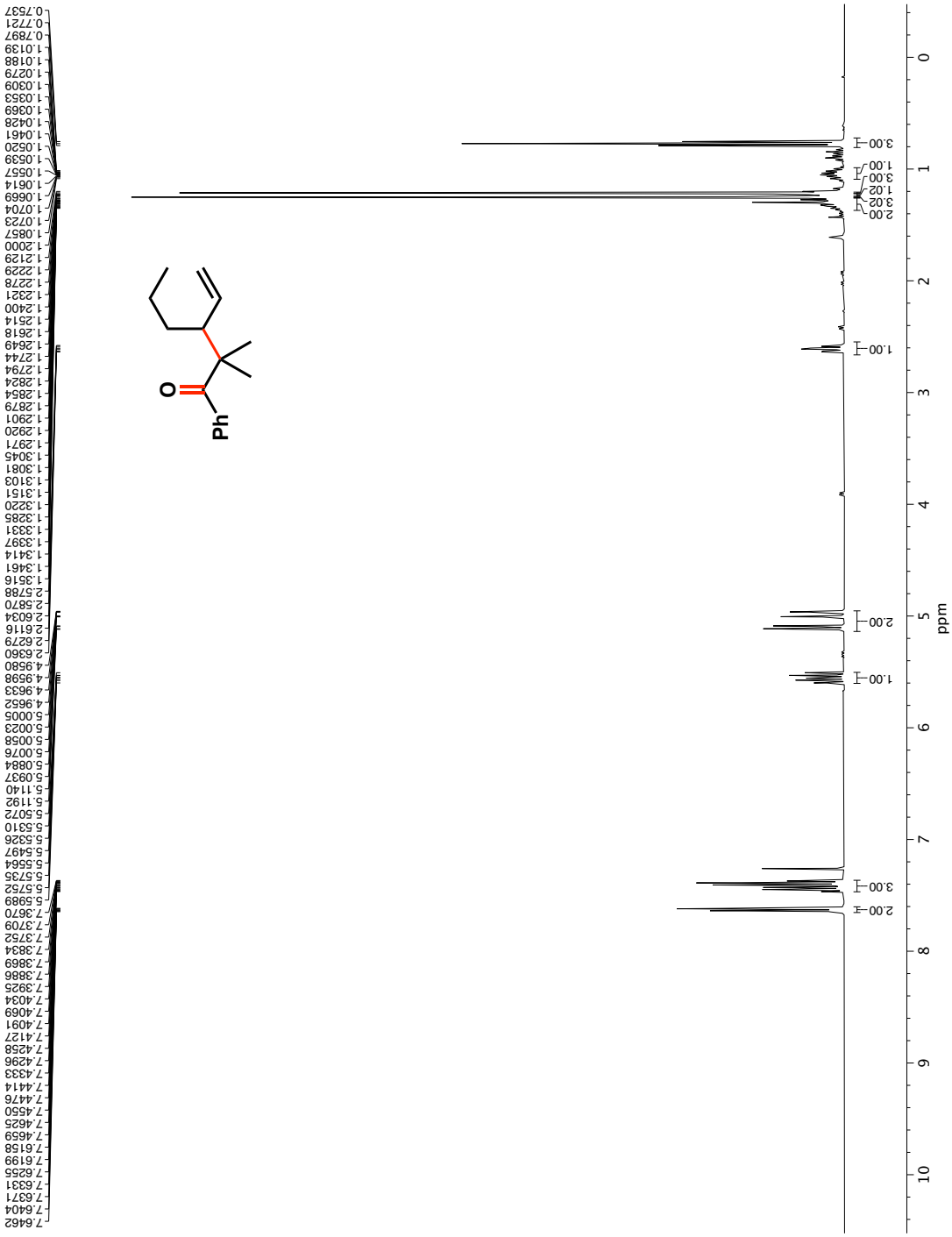
^{19}F NMR (282 MHz, $CDCl_3$) of compound **164b**.



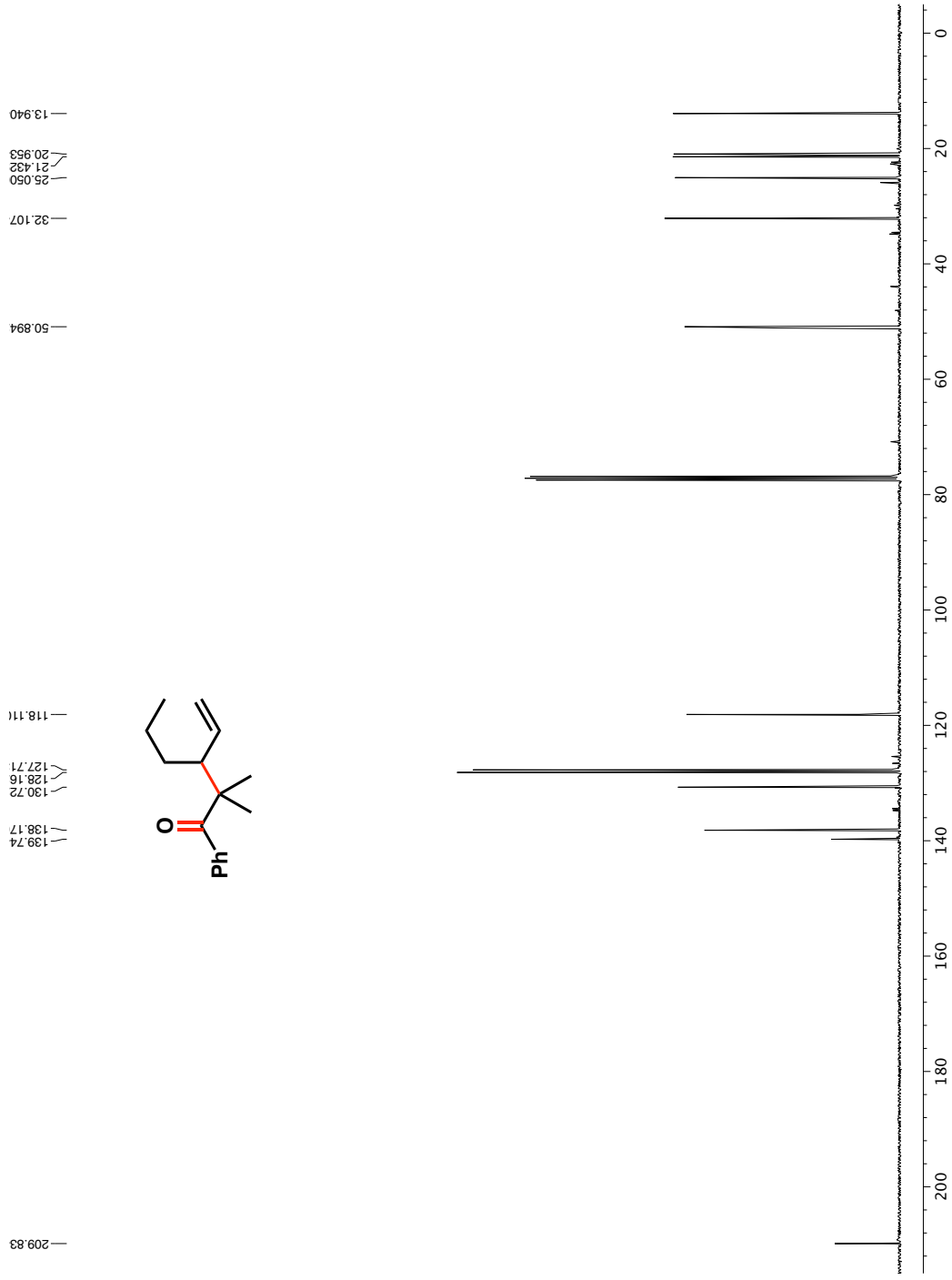
^{1}H NMR (400 MHz, $CDCl_3$) of compound **164c**.



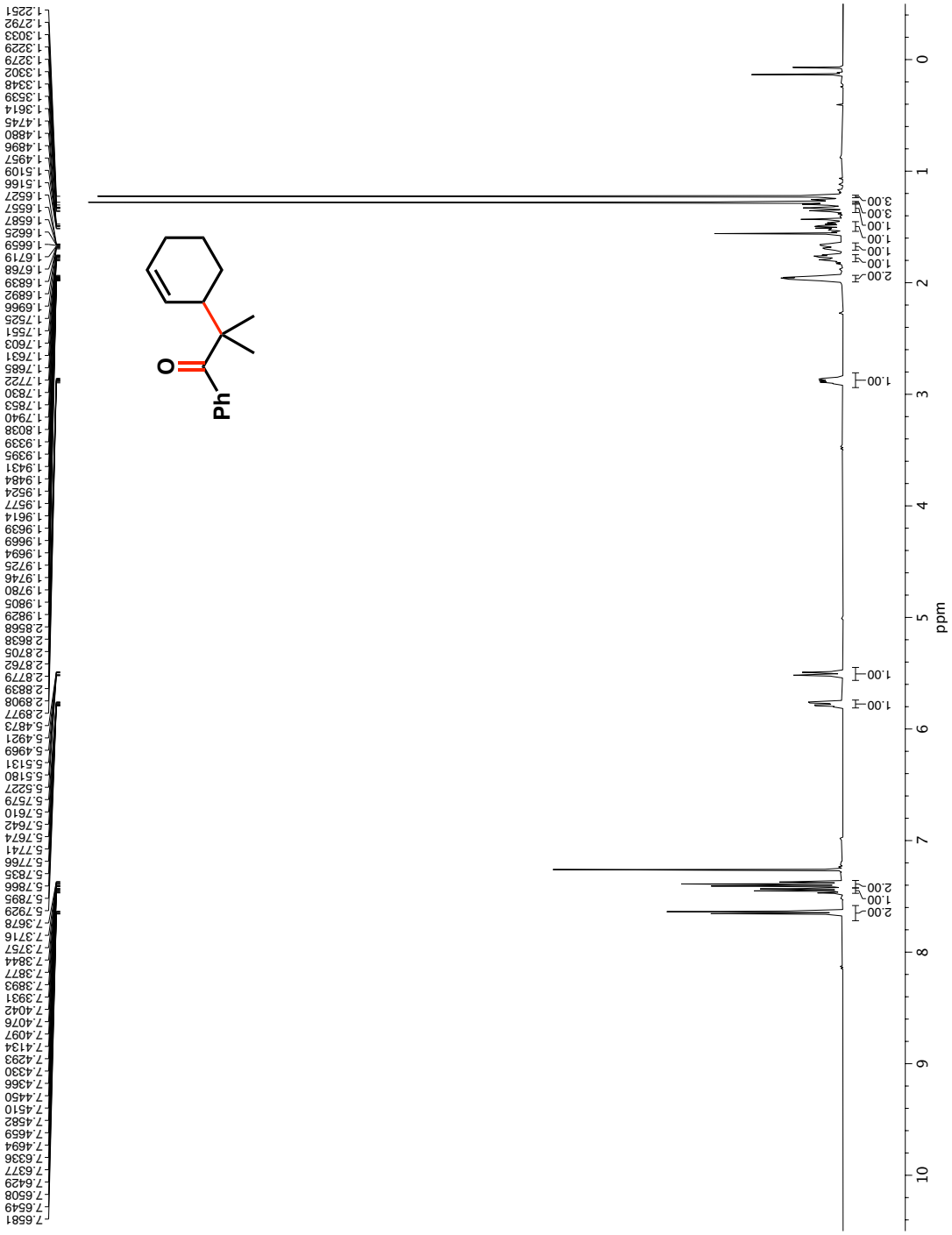
^{13}C NMR (101 MHz, $CDCl_3$) of compound **164c**.



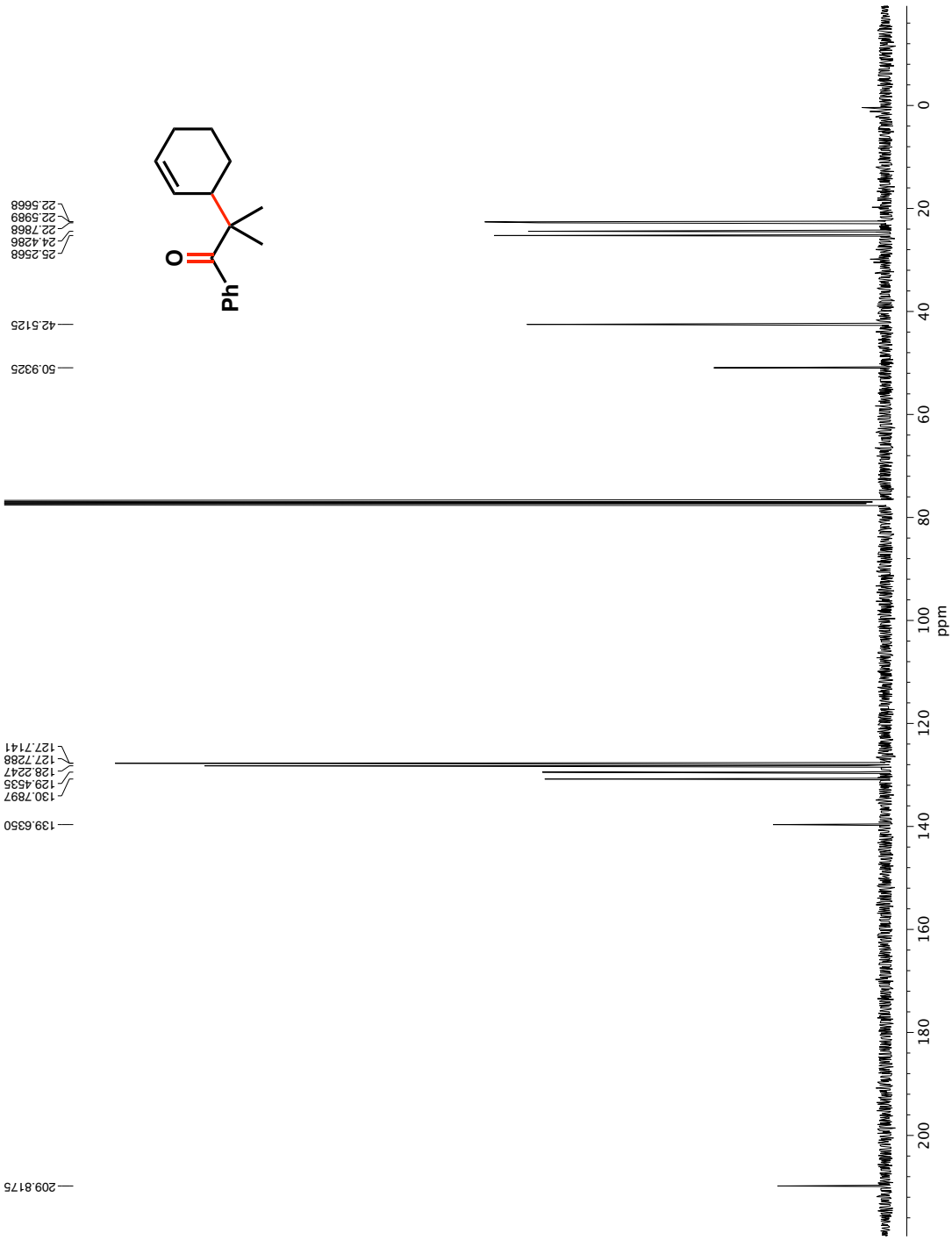
^{1}H NMR (400 MHz, $CDCl_3$) of compound **164d**.



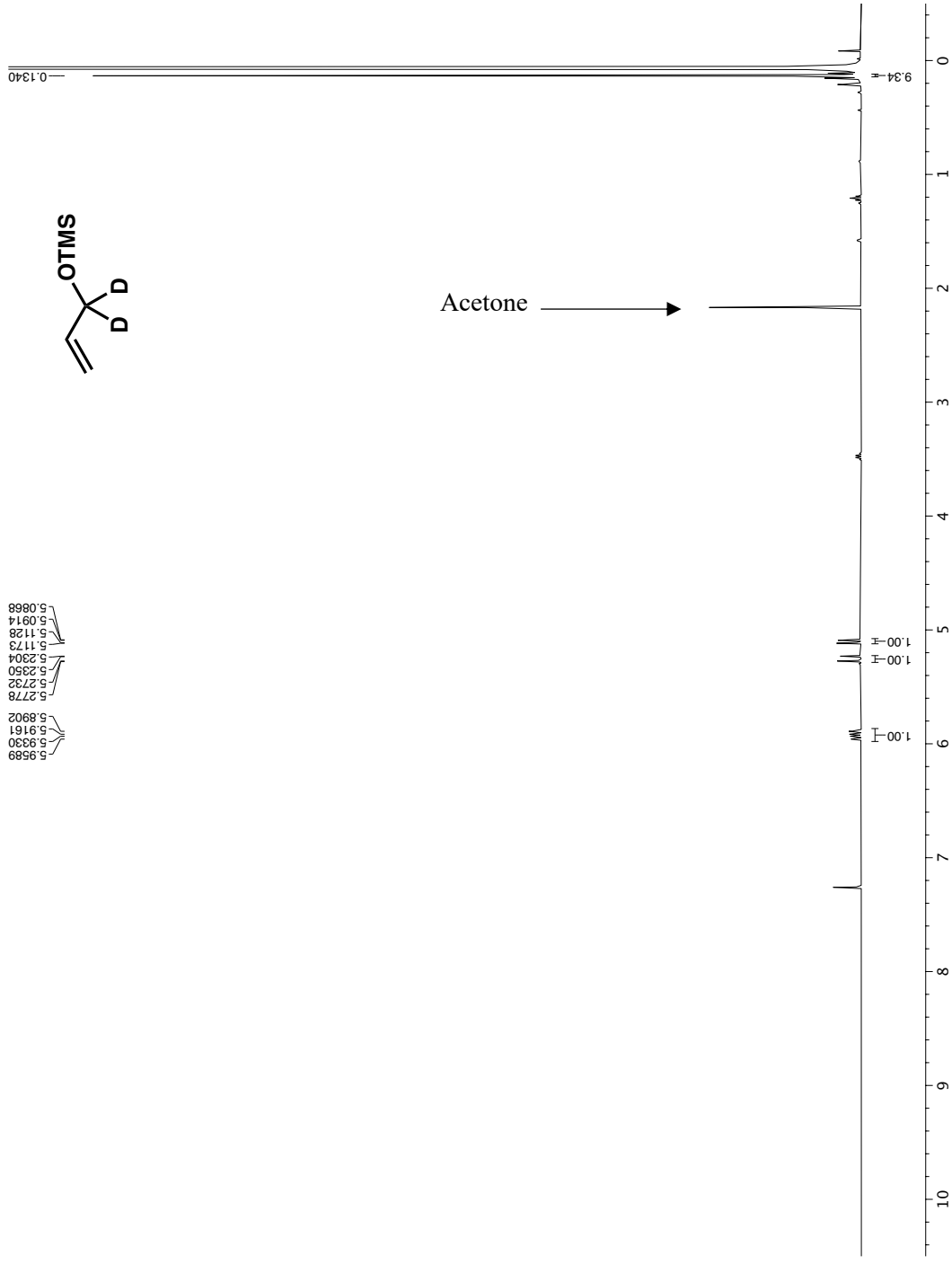
^{13}C NMR (101 MHz, $CDCl_3$) of compound **164d**.



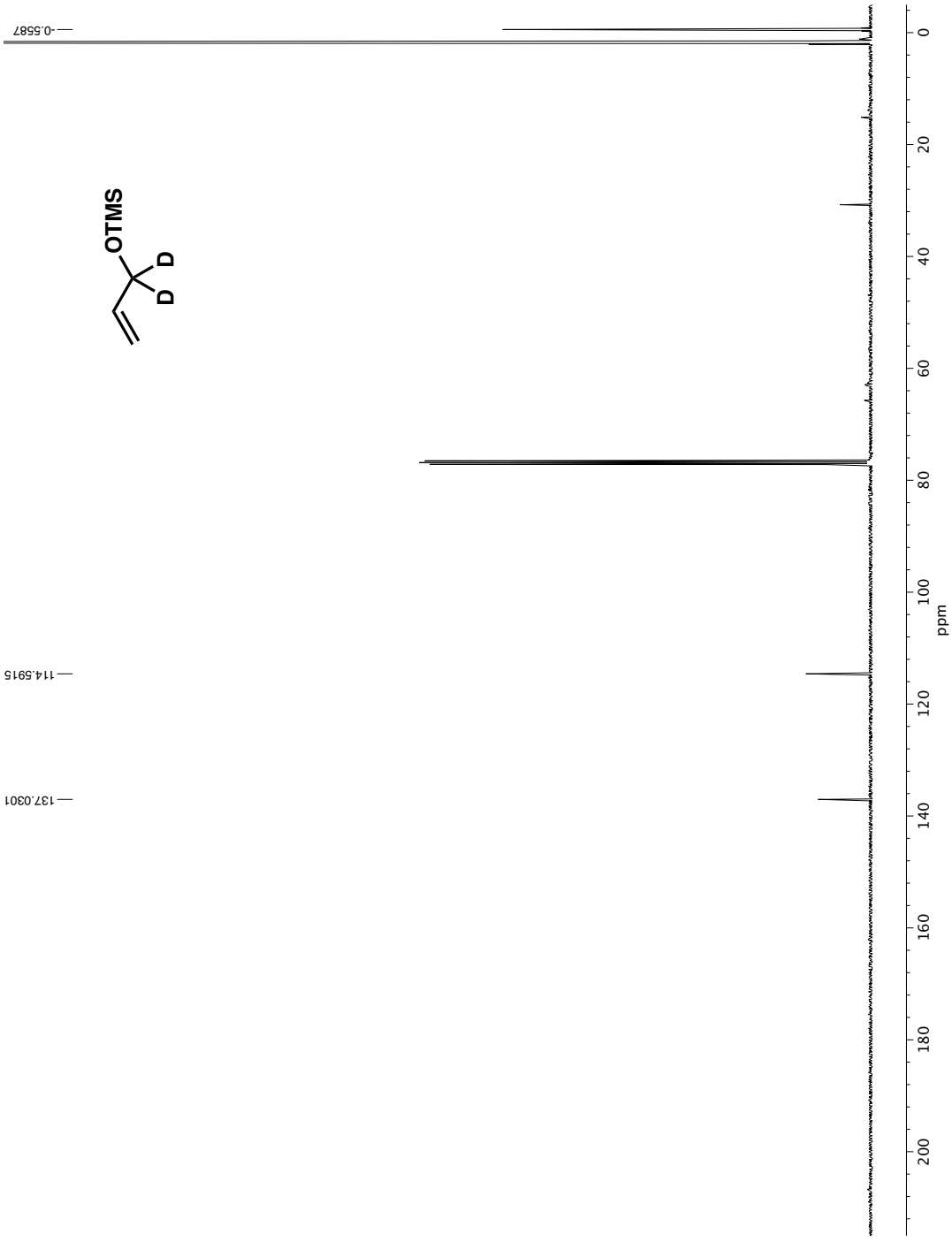
^{1}H NMR (400 MHz, $CDCl_3$) of compound **164e**.



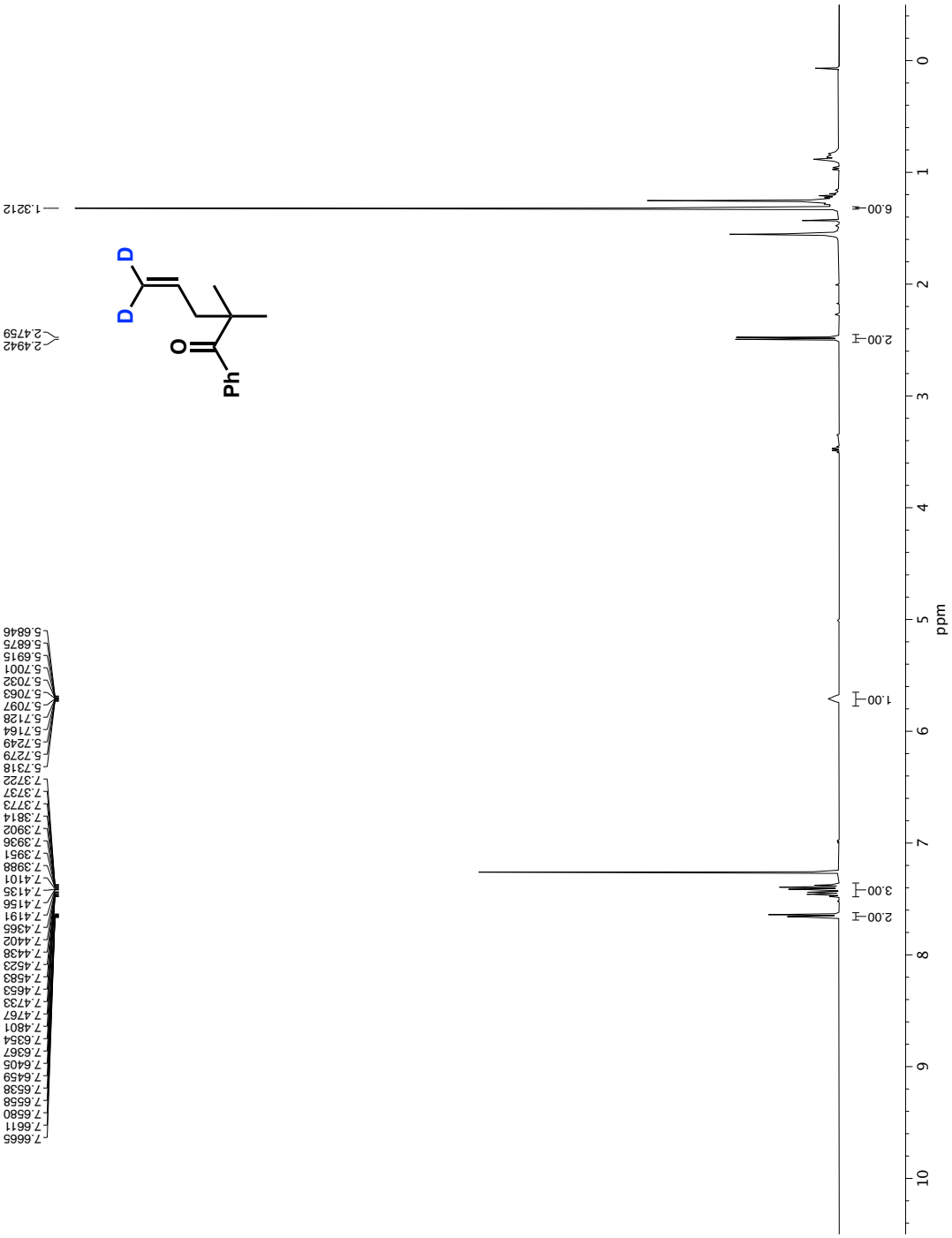
^{13}C NMR (101 MHz, $CDCl_3$) of compound **164e**.



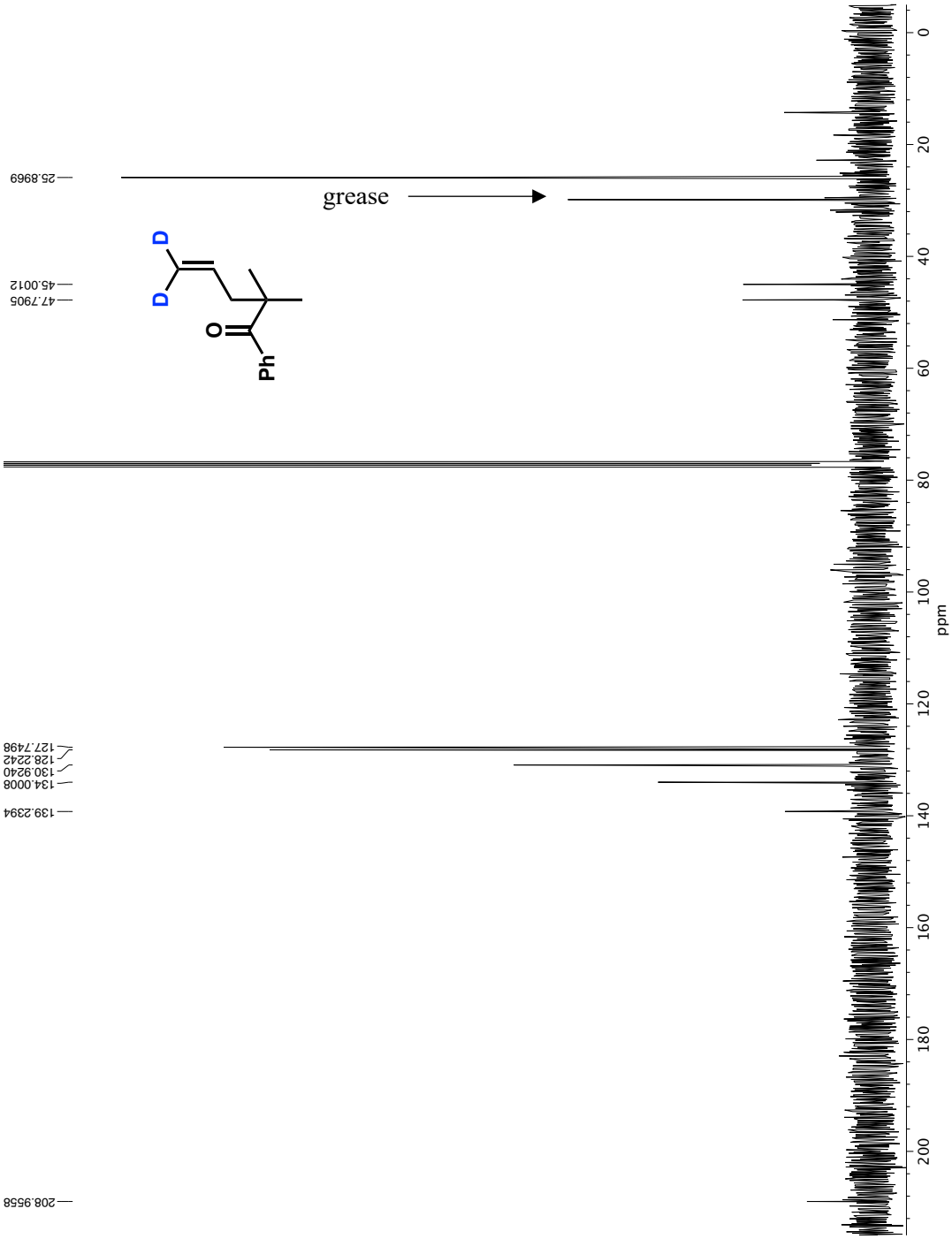
^{1}H NMR (400 MHz, $CDCl_3$) of compound **155-D_2**.



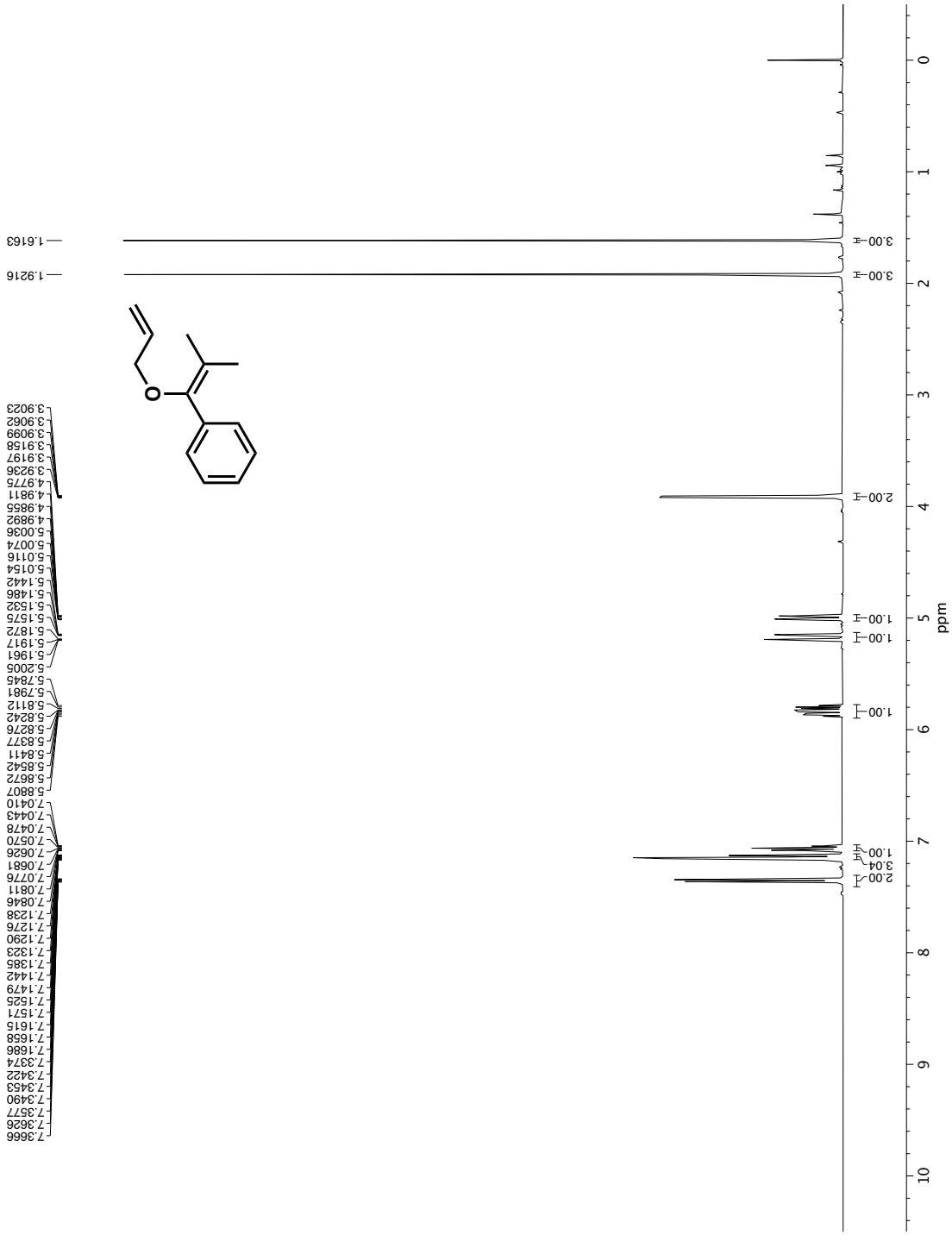
^{13}C NMR (101 MHz, $CDCl_3$) of compound **155-D_2**.



^{1}H NMR (400 MHz, $CDCl_3$) of compound **159-D_2**.



^{13}C NMR (101 MHz, $CDCl_3$) of compound **159-D_2**.



^{1}H NMR (400 MHz, $CDCl_3$) of compound **170**.

^{13}C NMR (101 MHz, $CDCl_3$) of compound **170**.

Chapter 4

Catalytic Asymmetric C–H Insertion Reactions of Vinyl Carbocations†

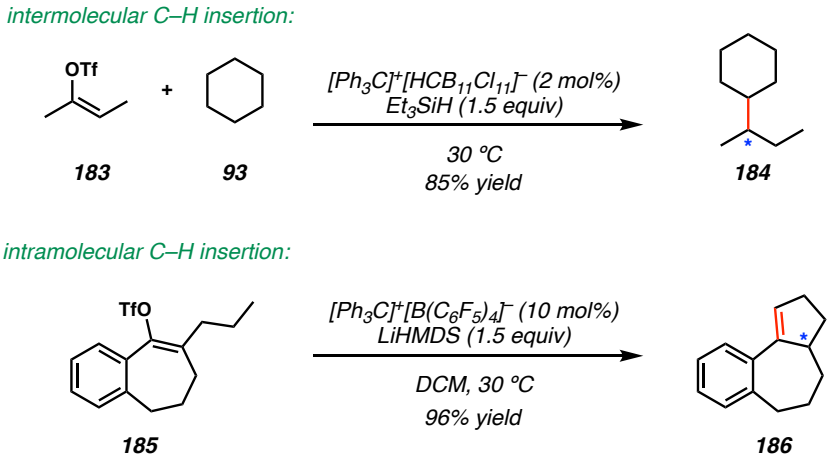
4.1 INTRODUCTION

Carbocationic intermediates play a crucial role in the synthesis of natural products and pharmaceutical drugs.[1] Although these reactive intermediates are engaged in stereoselective processes in nature,[2,3] exerting enantiocontrol over carbocations with synthetic catalysts remains challenging.[1] Typically, high levels of selectivity are only routinely seen in reactions of carbocations that are either resonance- or heteroatom-stabilized.[4–7] However, dicoordinated carbocations, such as aryl and vinyl cations, have thus far been excluded from the field of asymmetric catalysis, likely due to the lack of catalytic methods to generate these reactive intermediates and their high reactivity once

†Portions of this chapter have been adapted from Nistanaki, S. K.; Williams, C. G.; Wigman, B.; Wong, J. J.; Haas, B. C.; Popov, S.; Werth, J.; Sigman, M. S.; Houk, K.N.; Nelson, H. M. Catalytic asymmetric C–H insertion reactions of vinyl carbocations. *Science* **2022**, *378*, 1085–1091.

they are formed.[8] As briefly mentioned in Chapter 1, our group has developed catalytic methods to generate vinyl carbocations that are capable of undergoing facile insertion into unactivated C(sp^3)–H bonds (Scheme 4.1).[9,10] In these insertion reactions, stereocenters are often created (**184** and **186**), which prompted us to investigate their application in asymmetric catalysis.

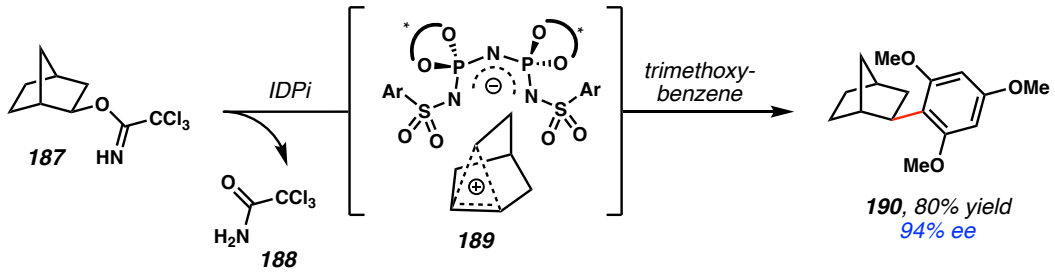
Scheme 4.1. *Stereocenters formed via C–H insertion reactions of vinyl cations.*



In addition to the inherent challenge of controlling the stereochemistry of a C–H insertion event involving a reactive vinyl cation intermediate, another challenge is the fact that these vinyl cations are generated catalytically using weakly coordinating anions (WCAs). These anions are non-basic and non-nucleophilic, which prevents unproductive E1 or S_N1 reactions of the vinyl cation intermediates.[11] Since there are only a few examples of chiral WCAs reported,[12,13] which have yet to be successful in asymmetric catalysis, we became interested in imidodiphosphorimidate (IDPi) Brønsted acids developed by List and coworkers for several reasons.[14] First, these IDPi acids are known to have a confined active

site that has been referred to as an enzyme mimic.[14] We believed this confinement effect could be vital to achieve high enantiocontrol over C–H insertion reactions of vinyl cations.[15,16] Additionally, the List group has also demonstrated success in employing these acids in highly enantioselective reactions that are proposed to proceed through carbocationic intermediates.[17,18] For example, protonation of **187** with an IDPi acid is proposed to form the non-classical cation paired with the IDPi chiral anion (**189**).[17] Due to the confinement of the cation within the IDPI active site, stereoselective reactions were achieved, such as a Friedel–Crafts reaction with 1,3,5-trimethoxybenzene to form **190** with high enantioselectivity (Scheme 4.2).

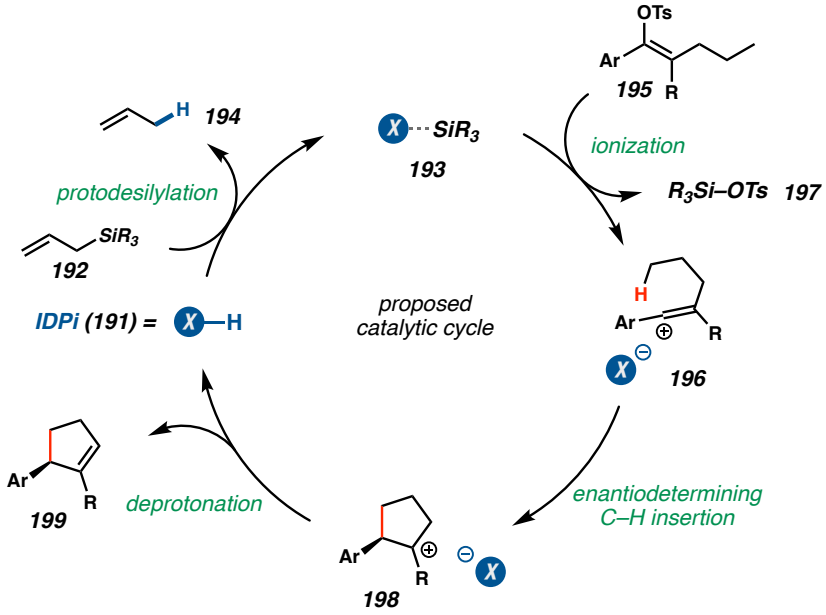
Scheme 4.2. *List's enantioselective reaction via non-classical carbocation.*



These IDPi acids have also been reported to undergo protodesilylation with allyl silanes to generate a silylated IDPI species, which can subsequently be used in enantioselective reactions via Lewis acid catalysis.[19] With this precedent, a proposed catalytic cycle for an enantioselective C–H insertion reaction is shown in Scheme 4.3. First, as supported by List and coworkers, IDPi Brønsted acid (**191**) can undergo protodesilylation with an allyl silane (**192**) to form the silylated IDPi **193** with the release of propene (**194**).[19] This species is then proposed to be sufficiently Lewis acidic to ionize

vinyl tosylate **195** to generate the vinyl cation/chiral anion pair (**196**). Then, due to the confined nature of the IDPi active site, an enantioselective C–H insertion event is proposed to form intermediate **198**. Deprotonation would result in product **199** with the regeneration of the IDPi acid (**191**).

Scheme 4.3. *Proposed catalytic cycle for enantioselective C–H insertion of vinyl cations using IDPi Brønsted acids.*



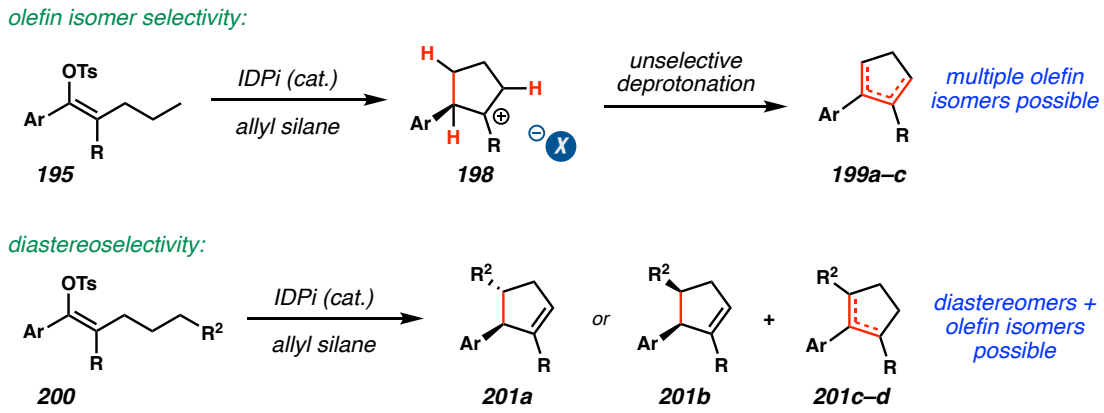
4.2 INVESTIGATION OF STRAINED-RING PRODUCT MOTIFS

4.2.1 Product Selectivity Challenges

While developing a highly selective C–H insertion reaction of vinyl carbocation intermediates, many substrates were investigated to achieve this goal. Like our reported C–H insertion reactions using WCAs,[9,10] unselective product formation was still a challenge. For example, unselective deprotonation of **198** can lead to multiple olefin isomers (**199a–**

c), and this was still true for using IDPi catalysts as the counter anion, where three different olefin isomers were often obtained (Scheme 4.4). In addition to olefin isomer selectivity, diastereoselectivity was also a challenge, which was further complicated by olefin isomer selectivity.

Scheme 4.4. *Challenges of olefin isomer selectivity and diastereoselectivity.*

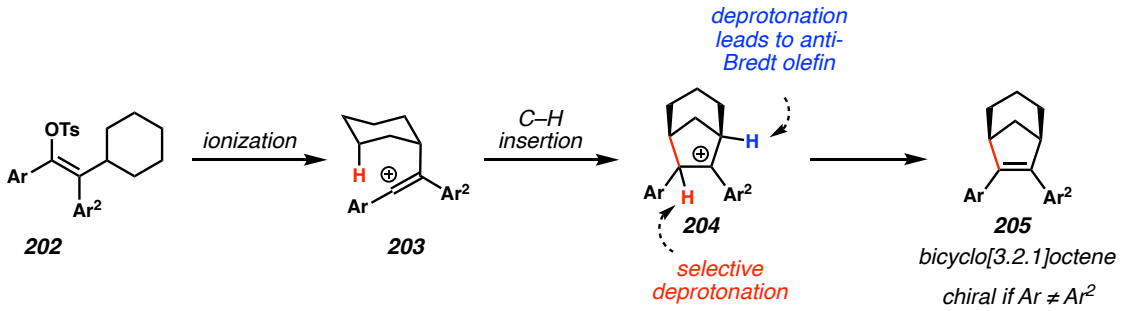


4.2.2 Investigation of Cyclohexyl Vinyl Tosylates

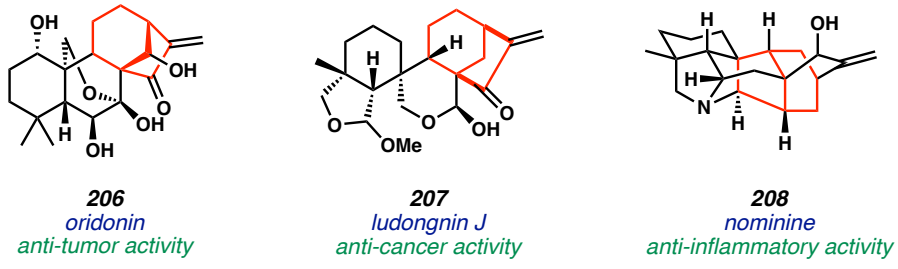
With the challenges of combatting not only enantioselectivity but also olefin isomer selectivity and diastereoselectivity, one class of substrates was particularly compelling. The use of cyclohexyl vinyl tosylate **202** was hypothesized to lead to selective product formation of a single olefin isomer and diastereomer (Scheme 4.5). Once the vinyl carbocation is formed (**203**), insertion into the cyclohexyl moiety would generate intermediate **204**. Given that deprotonation at the bridgehead carbon would lead to an anti-Bredt olefin isomer,[20] there is only one C–H bond that can be deprotonated to furnish strained-ring products **205**. Moreover, this C–H insertion event would allow direct access to the strained bicyclo[3.2.1]octane ring system, which are prevalent motifs in various

bioactive natural product scaffolds (**206**–**208**) (Scheme 4.6).[21–23]

Scheme 4.5. *C–H insertion to access [3.2.1]carbocycles.*



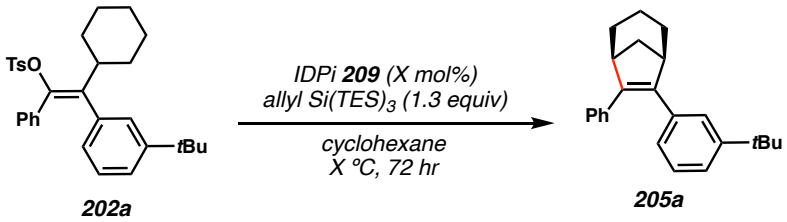
Scheme 4.6. *Natural products containing bicyclo[3.2.1]octanes.*



Given that a chiral product is only obtained with Ar ≠Ar^2 (Scheme 4.5), vinyl tosylate **202a** possessing an aryl group with a *m*-*t*-Bu substituent was prepared and screened, and it was found that bicyclic product **205a** could be formed (Table 4.1). **202a** was screened against various IDPi catalysts, and IDPi **209** possessing a *p*-Cl phenyl substituent on the 3,3' position of the BINOL scaffold proved to be the most promising. Reaction optimization thus commenced with IDPi **209** and tris(triethylsilyl) allylsilane (allyl Si(TES)$_3$, *vide infra*), and it was found that **205a** could be formed in 80% *ee*, albeit in 35% yield at 55 ºC (Table 4.1, entry 1). Given this promising enantioselectivity, efforts

were focused on increasing the yield of the reaction. Increasing the concentration of the reaction had minimal effect on the yield but did cause a slight decrease in enantioselectivity (entries 2 and 3). Decreasing the catalyst loading to 15 mol% at various concentrations also had little effect on the yield (entries 4 and 5). However, by raising the temperature from 55 ºC to 60 ºC at 0.025 M, the yield increased from 36% to 43% (entry 6). The yield was further improved by raising the temperature to 65 ºC, at which **205a** was formed in 50% yield and 77% *ee* (entry 7).

Table 4.1. *Reaction optimization of the synthesis of [3.2.1]carbocycles.*[a]

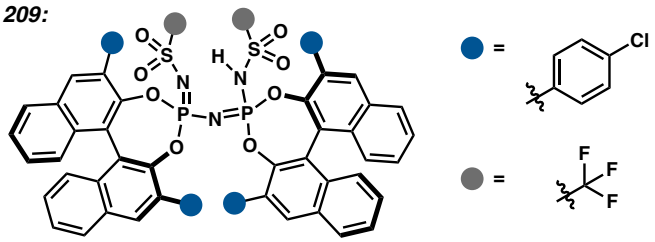


202a ***205a***

Entry	Catalyst	Temp. ºC	Conc. [SM]	Yield[a] (%)	%ee
1	*20 mol%*	*55 ºC*	*0.0125 M*	*35%*	*80%*
2	*20 mol%*	*55 ºC*	*0.025 M*	*35%*	*78%*
3	*20 mol%*	*55 ºC*	*0.05 M*	*32%*	*75%*
4	*15 mol%*	*55 ºC*	*0.025 M*	*36%*	*79%*
5	*15 mol%*	*55 ºC*	*0.05 M*	*40%*	*77%*
6	*15 mol%*	*60 ºC*	*0.025 M*	*43%*	*77%*
7	*15 mol%*	*65 ºC*	*0.025 M*	*50%*	*77%*
8	*0 mol%*	*65 ºC*	*0.025 M*	*0%*	–

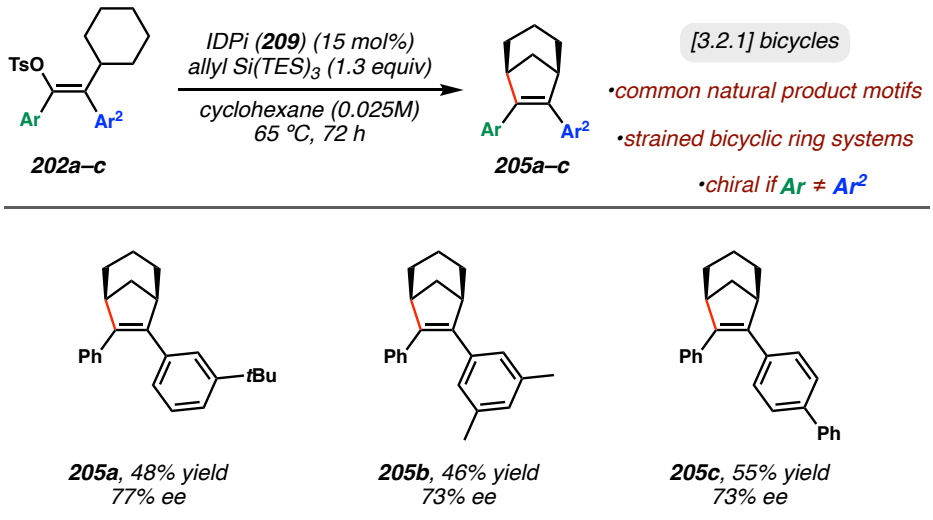
[a]*Yields determined by ^{1}H NMR using $MeNO_2$ as an internal standard.*

IDPi 209:



After the reaction was optimized, vinyl tosylates **202b** and **202c** were prepared and subjected to the reaction conditions (Scheme 4.7). Product **205b** was isolated in 46% yield with 73% *ee*. Obtaining this level of enantioselectivity on this all-hydrocarbon substrate was quite encouraging, as the only differentiating features between the two aryl rings were two dimethyl substituents. Additionally, biphenyl vinyl tosylate **202c** furnished the strained ring **205c** in 55% yield with 73% *ee*. Overall, accessing these strained ring products not only demonstrated that moderate levels of enantioselectivity could be obtained with all hydrocarbon scaffolds but also showed that C–H insertion reactions of vinyl cations is a powerful C–C bond forming strategy for the construction of challenging ring systems.

Scheme 4.7. *Catalytic asymmetric synthesis of strained bicycles.*[a]

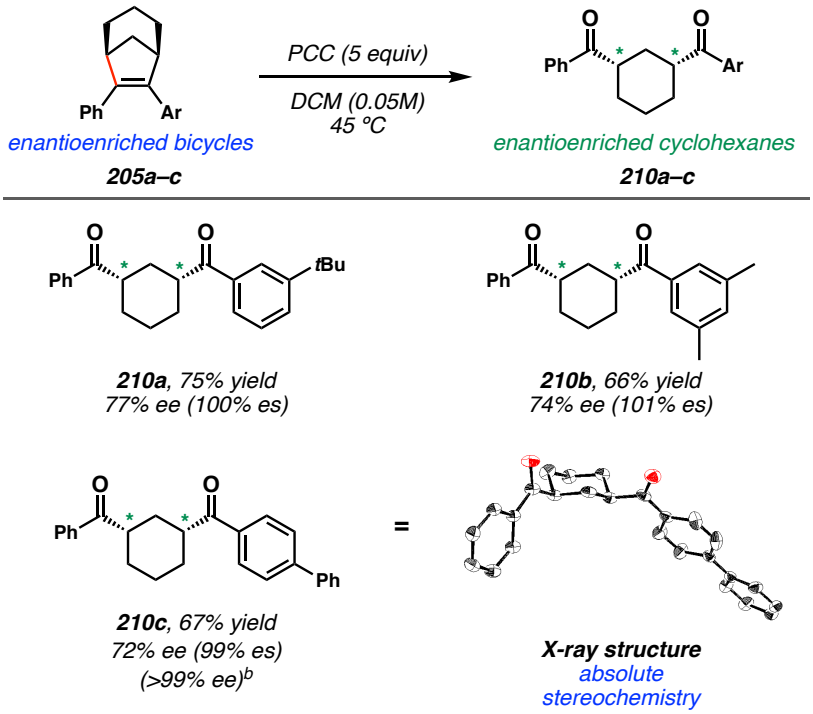


[a]Isolated yield after column chromatography on 0.15 mmol scale.

4.2.3 Product Elaboration of [3.2.1] Carbocycles

Given the high energy of the strained [3.2.1] carbocycles and potential for further reactivity, it was hypothesized that perhaps these enantioenriched products could be elaborated to generate other useful enantioenriched motifs. In particular, upon oxidation of the strained olefin,[24] the ring could cleave to furnish enantioenriched 1,3-diketocyclohexanes **210a–c** (Scheme 4.8). It was found that by subjecting **205a–c** to pyridinium chlorochromate (PCC) in DCM and heating at 45 ºC, enantioenriched cyclohexanes **210a–c** could be obtained in good yields. Notably, the products possessed excellent enantiospecificity (es). Additionally, **210c** was isolated as a solid and upon recrystallization, highly enantioenriched material (>99% *ee*) was obtained. With the recrystallized material in hand, an X-ray structure was obtained, further confirming the identity of the products and indicating the absolute stereochemistry. Current catalytic methods to access enantioenriched 1,3-diketocyclohexanes are limited to desymmetrization of anhydrides, after which additional steps are required to convert the resulting carboxylic acid to scaffolds such as **210a–c**,[25] highlighting a strategic application of this reaction.

Scheme 4.8. *Product elaboration to enantioenriched 1,3-diketocyclohexanes.*[a]



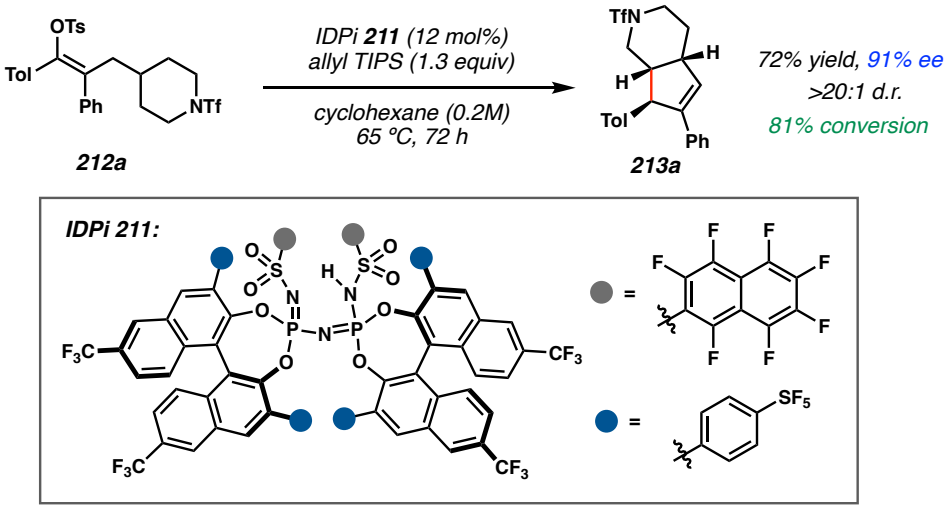
[a]Isolated yield after column chromatography on 0.05 mmol scale. [b]After single recrystallization.

4.3 ENANTIOSELECTIVE C–H INSERTION REACTIONS OF PIPERIDINE SUBSTRATES

4.3.1 Reaction Optimization

Concurrently during the exploration of the C–H insertion reaction to generate bicyclo[3.2.1]cycles, other substrates were still being explored and optimized in efforts to access highly enantioenriched products. It was discovered that by using IDPi **211** and allyltriisopropylsilane (allyl TIPS), the vinyl tosylate **212a**, possessing an appended piperidine fragment, could furnish bicycle product **213a** in 72% yield and 91% *ee*. Notably, the product was formed with excellent diastereoselectivity (>20:1 *d.r.*) and olefin isomer selectivity that favored selective formation of the trisubstituted olefin isomer (Scheme 4.9).

Scheme 4.9. *Enantioselective C–H insertion reaction of piperidine substrate.*

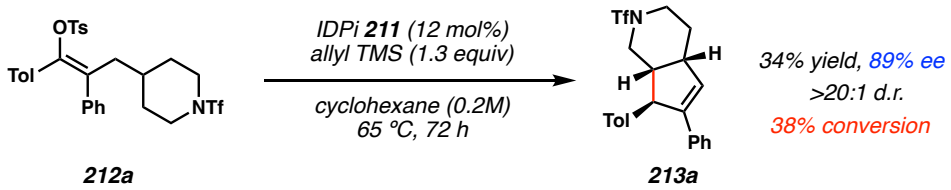


Although the yield was satisfactory (72% yield) for **213a**, conversion of starting material was still only about 81% after 72 hours due to the poor activity of IDPi **211**. Moreover, it was a concern that more electron-poor substrates (i.e. substrates with higher barriers for ionization) resulted in significantly lower yield than vinyl tosylate **212a**. With that in mind, efforts were focused on optimizing the reaction further to obtain higher conversion without losing enantioselectivity.

Based on our proposed mechanism (Scheme 4.3), we hypothesized that conversion of the reaction could be improved by tuning the silyl group on the allyl silane, given that the silylated IDPi (**193**) was likely the active catalyst in the reaction. At first, we proposed that perhaps conversion was low due to the bulkiness of the TIPS group on the allyl silane, which caused steric hinderance around the silicon center and thus made ionization more challenging. Therefore, allyl trimethylsilane (allyl TMS) was tested. To our surprise, the yield of **213a** was dramatically worse, forming the product in only 34% yield (38% conversion) after 72 hours. Luckily, the enantioselectivity was not dramatically influenced

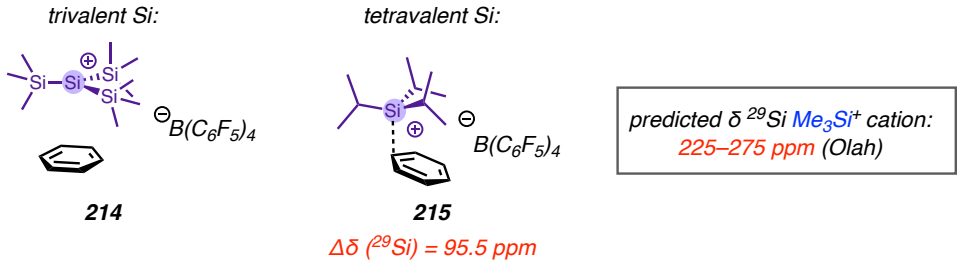
(Scheme 4.10).

Scheme 4.10. *Allyl TMS leads to poor conversion of vinyl tosylate.*



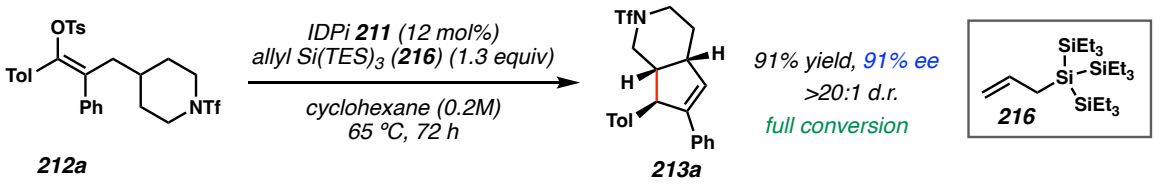
With allyl TMS negatively impacting reaction conversion, we decided to move in the opposite direction and test allyl silanes that were even more sterically congested than allyl TIPS. We were inspired by Lambert's studies on the effects of steric bulk on silylium ion coordination, wherein $Si(TMS)_3^+$ (**214**) paired with a WCA generated a near trivalent silylium cation, in contrast to trialkyl silylium cation **215**, which formed a tetravalent Si-center by coordination to solvent or counter anion (Scheme 4.11).[26,27] Moreover, these results were also consistent with the δ ^{29}Si that Olah had predicted for a trivalent Me_3Si^+ species.[28] We hypothesized that a more trivalent silylium species may possess stronger Lewis acidity, and thus may enhance reaction rates due to more facile ionization to generate vinyl cations.

Scheme 4.11. *Trivalent silicon centers with bulky tris(silyl) groups.*



Therefore, allyl $Si(TES)_3$ (**216**) was prepared and tested. Gratifyingly, in our system, we observed a positive correlation between silane size and activity, and **212a** was fully consumed after 72 hours to afford **213a** in 91% yield with 91% *ee* (Scheme 4.12).

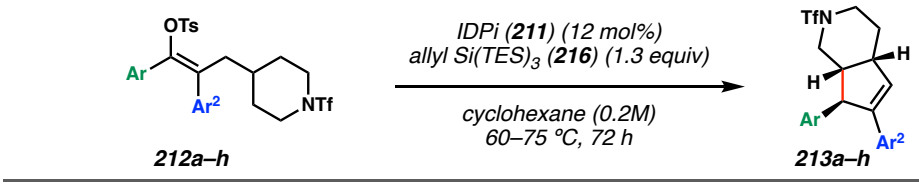
Scheme 4.12. *Allyl $Si(TES)_3$ leads to full conversion.*

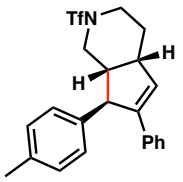


4.3.2 Examples of Enantioselective C–H Insertion Reaction

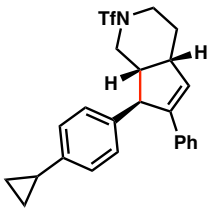
With this improved activity from allyl $Si(TES)_3$ and encouraging enantioselectivity on our model substrate, we explored the scope of this reaction with selected examples displayed in Scheme 4.13. The transformation proved compatible with substitution at both of the aryl rings on the substrate, delivering insertion products in moderate to good yields with excellent enantioselectivity (up to 93% *ee*) and diastereoselectivity (>20:1 *d.r.*). In addition to alkyl substituents on the phenyl ring of vinyl tosylates **212a–c**, both electron-withdrawing and electron-donating groups were also tolerated (**212d–f**). Additionally, a single recrystallization of **213d** resulted in highly enantioenriched material (>99% *ee*). Moreover, functional groups labile in many transition metal-catalyzed processes (**213g, 213h**) were compatible, highlighting this method's complementarity to transition metal-catalyzed C(sp^3)–H functionalization platforms.

Scheme 4.13. *Enantioselective C–H insertion reaction of piperidine substrates.*

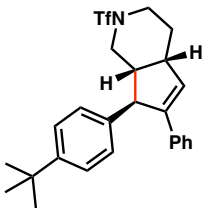




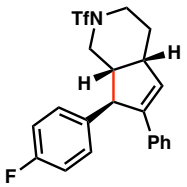
***213a**, 81% yield*
>20:1 d.r.
91% ee



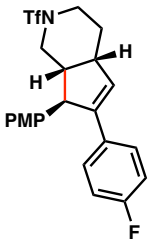
***213b**, 81% yield*
>20:1 d.r.
92% ee



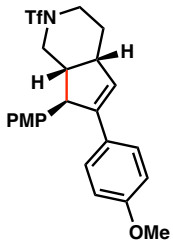
***213c**, 95% yield*
>20:1 d.r.
88% ee



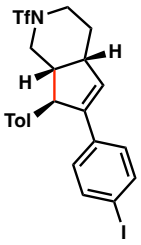
***213d**[b], 57% yield*
>20:1 d.r.
87% ee (99% ee)[c]



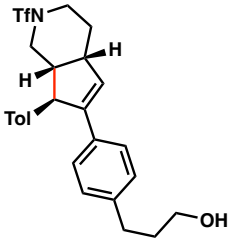
***213e**[d], 78% yield*
>20:1 d.r.
91% ee



***213f**[d], 60% yield*
>20:1 d.r.
93% ee



***213g**, 54% yield*
>20:1 d.r.
90% ee



***213h**[e], 64% yield*
>20:1 d.r.
87% ee

[a]Isolated yield after column chromatography on 0.20 mmol scale. [b]96 hr at 75 °C. [c]After single recrystallization. [d]0.1M. [e]2.3 equiv of silane used and crude reaction then stirred with tetrabutylammonium fluoride.

4.4 CONCLUDING REMARKS

In conclusion, we developed a highly enantioselective C–H insertion reaction of vinyl cations. This work represents the first example of controlling the enantioselectivity of a reaction proceeding through these dicoordinated carbocations. Ultimately, this was successful through the use of confined IDPi Brønsted acids, which generated a silylium species Lewis acidic enough to ionize vinyl tosylates. Two different classes of substrates were optimized, suggesting that this reaction platform could be further applied to other types of substrates to access other C–H insertion products with good selectivity.

4.5 EXPERIMENTAL SECTION

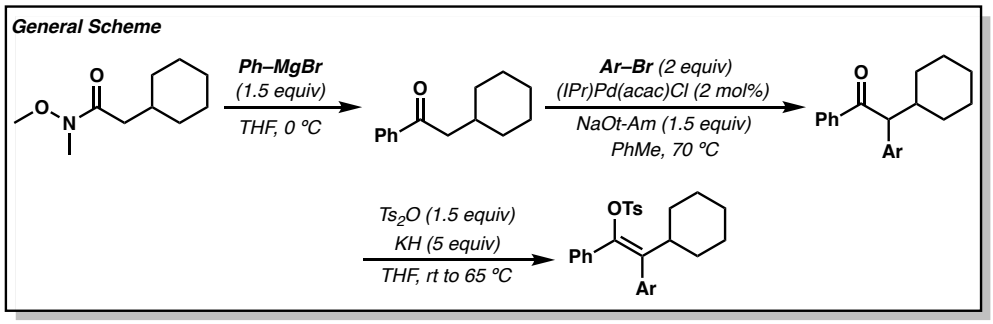
4.5.1 Materials and Methods

Unless otherwise stated, all reactions were performed in an MBraun glovebox under nitrogen atmosphere with ≤ 0.5 ppm O_2 levels. All glassware and stir-bars were dried in a 160 °C oven for at least 12 hours and cycled directly into the glovebox for use. Solid substrates were dried on high vacuum over P_2O_5 overnight. All solvents were rigorously dried before use. Cyclohexane was distilled over potassium. *o*-Difluorobenzene was distilled over CaH_2. 1,2-Dichloroethane and trifluorotoluene were degassed and dried in a JC Meyer solvent system and stored inside a glovebox. All other solvents used for substrate synthesis were dried in a JC Meyer solvent system. Silanes were dried by distillation over CaH_2 or dried on high vacuum over P_2O_5 overnight before being stored in a glovebox. Triethylamine and diisopropylamine were distilled over CaH_2 prior to use. Tf_2O was purified by distillation over P_2O_5. Preparatory thin layer chromatography (TLC) was performed using Millipore silica gel 60 F_{254} pre-coated plates (0.25 mm) and visualized by UV fluorescence quenching. SiliaFlash P60 silica gel (230-400 mesh) was used for flash chromatography. Purification by preparative HPLC was done on an Agilent 1200 series instrument with a reverse phase Alltima C_{18} (5μ, 25 cm length, 1 cm internal diameter) column. Measurements of enantiomeric excess (*% ee*) were performed using an Agilent 1260 infinity chiral HPLC using Daicel CHIRALPAK® or Daicel CHIRALCEL® columns (4.6 × 250mm, 5 μm particle size) and hexanes/isopropanol as the mobile phase. NMR spectra were recorded on a Bruker 400 MHz with Prodigy cryoprobe (^{1}H, ^{13}C, ^{31}P, ^{11}B), a Bruker 400 MHz (^{1}H, ^{13}C, ^{19}F) and a Varian 300 MHz (^{1}H, ^{19}F). ^{1}H NMR spectra are reported relative to $CDCl_3$ (7.26 ppm), C_6D_6 (7.16 ppm), d_6-Acetone (2.05 ppm), or d_6-

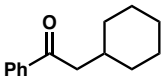
DMSO, (2.50 ppm) unless noted otherwise. Data for ^{1}H NMR spectra are as follows: chemical shift (ppm), multiplicity, coupling constant (Hz), integration. Multiplicities are as follows: s = singlet, d = doublet, t = triplet, dd = doublet of doublet, dt = doublet of triplet, ddd = doublet of doublet of doublet, td = triplet of doublet, m = multiplet. ^{13}C NMR spectra are reported relative to $CDCl_3$ (77.1 ppm), C_6D_6 (128.0 ppm), d_6-Acetone (29.8 ppm), or d_6-DMSO (39.5 ppm) unless noted otherwise. IR Spectra were record on a Perkin Elmer Spectrum BXII FT-IR spectrometer and are reported in terms of frequency absorption (cm^{-1}). High resolution mass spectra (HR-MS) were recorded on an Agilent 6230 time-of-flight LC/MS (LC/TOF) using electrospray ionization (ESI) or acquired by the Caltech Mass Spectral Facility on a JEOL JMS-T2000 AccuTOF GC-Alpha time-of-flight mass spectrometer using Field Desorption (FD) ionization or an electron ionization source. Crystallographic data were obtained by the Beckman Institute Crystallography Facility and by the UCLA J.D. McCullough Laboratory of X-ray Crystallography. All commercial chemicals and reagents were used as received, unless otherwise noted. KOtBu, Ts_2O (97%), and 4-chloroboronic acid were purchased form Sigma-Aldrich and used as received. Bromomethyl methyl ether (MOM-Br) was ordered from Oakwood Chemicals and distilled before used. 1,1'-Bi-2-naphthol (R & S), EDCI, diiodine, 4-piperidinemethanol, Tf_2O, imidazole, triphenylphosphine, DMAP, N,O-dimethylhydroxylamine hydrochloride, 2-phenylacetophenone, cyclohexylacetic acid, tert-butyl 4-(hydroxymethyl)piperidin-1-carboxylate, octafluoronaphthalene, pentachlorobenzenethiol, trifluoromethanesulfonamide, methyl 2,2-difluoro-2-(fluorosulfonyl)acetate, and sodium pentoxide were all ordered from Oakwood chemicals and used as received.

4.5.2 Preparation of Vinyl Tosylates

Scheme for the synthesis of cyclohexyl vinyl tosylate substrates:



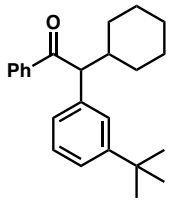
The general procedure outlined above was used to prepare diaryl cyclohexyl vinyl tosylate substrates from cyclohexyl acetic acid-derived Weinreb amide, which was prepared according to a published procedure.[29] The tosylation step generates the *E* isomer shown as the major isomer, but some *Z* isomer is also produced, which is typically more polar in R_f and could be separated out via column chromatography. While both the *Z* and *E* isomer of the vinyl tosylate give similar results in C–H insertion reactions (activity and enantioselectivity), only the *E* isomer was used for experiments. *If the vinyl tosylate is impure after column chromatography, pure material could be obtained via recrystallization from hexanes/ethyl acetate or hexanes/diethyl ether.



2-cyclohexyl-1-phenylethan-1-one (214)

Magnesium turnings (1.97 g, 1.5 equiv, 81.0 mmol) were flame-dried under high vacuum in a round bottom flask (x3) then suspended in dry THF (81 mL). Bromobenzene (10.7 mL, 1.9 equiv, 102.6 mmol) was added followed by a small grain of I_2. The solution was allowed to stir with gentle heating *via* a heat gun until the purple-brown color of the I_2

disappears. The suspension was then stirred until all the magnesium turnings are visibly consumed. At this point, the reaction is cooled to 0 ºC then a solution of 2-cyclohexyl-N-methoxy-N-methylacetamide[29] (10.0 g, 1.0 equiv, 54.0 mmol) in dry 180 mL THF is added dropwise. The reaction was monitored closely by TLC to determine starting material consumption (usually 5–20 minutes), then quenched with 30 mL saturated ammonium chloride while at 0 ºC. The reaction was extracted with ethyl acetate (x3), then the combined organics were washed with water, brine, dried over Na_2SO_4, and concentrated *in vacuo*. Pure material was obtained *via* silica flash column chromatography (20% ethyl acetate/hexanes), furnishing ketone **214** as a colorless oil (9.5 g, 87%), and NMR data matched the published spectra.[30]



2-(3-(*tert*-butyl)phenyl)-2-cyclohexyl-1-phenylethan-1-one (215)

Following a slightly-modified reported procedure[31]: To a flame-dried Schlenk flask was added (IPr)Pd(acac)Cl (93.4 mg, 0.02 equiv, 0.15 mmol) and sodium *t*-pentoxide (1.22 g, 1.5 equiv, 11.1 mmol), and these solids were vac/backfilled with N_2 (x3). Anhydrous PhMe was then added (7.5 mL), followed by commercially available 1-bromo-3-(*tert*-butyl)benzene (2.6 mL, 2.0 equiv, 14.8 mmol) and ketone **214** (1.50 g, 1.0 equiv, 7.41 mmol). The Schlenk flask was then sealed and heated to 70 ºC. When the reaction reached completion (usually 12–14 hours later), the reaction was cooled to room temperature and diluted with water. The solution was extracted with diethyl ether (x3), and the organics

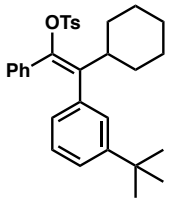
were then washed with brine and dried with $MgSO_4$ and concentrated *in vacuo*. Pure material was *via* flash column chromatography (2→3% ether/hexanes), furnishing ketone **215** as a yellow oil (1.2 g, 48% yield).

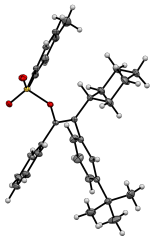
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.95 (m, 2H), 7.50 – 7.46 (m, 1H), 7.42 – 7.37 (m, 2H), 7.34 (q, *J* = 1.5 Hz, 1H), 7.24 – 7.18 (m, 2H), 7.14 (dt, *J* = 6.1, 2.4 Hz, 1H), 4.30 (d, *J* = 10.2 Hz, 1H), 2.35 – 2.23 (m, 1H), 1.87 – 1.80 (m, 1H), 1.69 – 1.61 (m, 3H), 1.29 (m, 11H), 1.12 (s, 2H), 1.01 – 0.92 (m, 1H), 0.84 (td, *J* = 13.1, 10.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.0, 151.6, 138.1, 137.7, 132.8, 128.6, 128.6, 128.3, 126.3, 126.0, 123.9, 60.5, 41.3, 34.8, 32.8, 31.5, 30.9, 26.7, 26.4, 26.3.

FT-IR (neat film NaCl): 2925, 2851, 1678, 1597, 1447, 1200, 690 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{24}H_{31}O$: 335.2375; Measured: 355.2369.





(*E*)-2-(3-(tert**-butyl)phenyl)-2-cyclohexyl-1-phenylvinyl 4-methylbenzenesulfonate (202a)**

To a flame-dried Schlenk flask was added 30% Wt KH (2.28 g, 5 equiv, 17.04 mmol) then suspended in THF (8 mL). In a separate flask, a solution of ketone **215** (1.14 g, 1.0 equiv, 3.41 mmol) in THF (4 mL) was prepared and added dropwise to the KH suspension. The flask was then sealed and heated to 60 ºC for 7 hr. Then, the enolate solution was cooled to room temperature and Ts_2O (1.67 g, 1.5 equiv, 5.11 mmol) was added at once to the

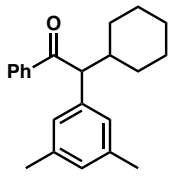
enolate solution with vigorous stirring (solution turns thick). Once the reaction was completed by TLC analysis (10% ether/hexanes), the reaction was quenched with water very slowly and extracted with ethyl acetate (x3). The combined organics were washed once with brine, dried over Na_2SO_4, filtered, concentrated in vacuo, and purified by silica flash column chromatography (8% diethyl ether/hexanes) to yield vinyl tosylate **202a** as a white solid (600 mg, 36% yield). The olefin isomer was confirmed to be *E* on the basis of X-ray crystallographic analysis.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.46 (m, 2H), 7.16 – 7.05 (m, 4H), 6.95 – 6.88 (m, 2H), 6.88 – 6.82 (m, 4H), 6.80 (dt, J = 7.4, 1.5 Hz, 1H), 2.99 (tt, J = 12.0, 3.1 Hz, 1H), 2.36 (s, 3H), 1.68 (ddt, J = 9.9, 6.6, 3.5 Hz, 4H), 1.60 (s, 1H), 1.35 – 1.26 (m, 2H), 1.14 (s, 9H), 1.08 (td, J = 12.9, 4.0 Hz, 2H), 1.02 – 0.95 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4, 144.5, 142.6, 140.6, 136.2, 134.6, 134.4, 129.7, 129.4, 128.4, 128.2, 127.3, 127.21, 127.18, 127.21, 123.4, 40.0, 34.5, 31.2, 31.1, 26.5, 25.9, 21.7.

FT-IR (neat film NaCl): 2926, 2853, 1599, 1450, 1372, 1189, 1177, 1094, 1003, 970, 913, 842, 804, 783, 711 cm^{-1}.

HR-MS (ESI) m/z: [M+Na]+ Calculated for $C_{31}H_{36}NaO_3S$: 511.2277; Measured: 511.2286.



2-cyclohexyl-2-(3,5-dimethylphenyl)-1-phenylethan-1-one (216)

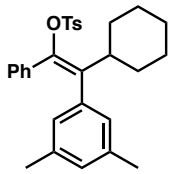
Following a slightly-modified reported procedure[31]: To a flame-dried Schlenk flask was added (IPr)Pd(acac)Cl (93.4 mg, 0.02 equiv, 0.15 mmol) and sodium *t*-pentoxide (1.22 g, 1.5 equiv, 11.1 mmol), and these solids were vac/backfilled with N_2 (x3). Anhydrous PhMe was then added (7.5 mL), followed by commercially available 1-bromo-3,5-dimethylbenzene (2.0 mL, 2.0 equiv, 14.8 mmol) and ketone **214** (1.50 g, 1.0 equiv, 7.41 mmol). The Schlenk flask was then sealed and heated to 70 ºC. When the reaction reached completion (usually 12–14 hours later), the reaction was cooled to rt and diluted with water. The solution was extracted with diethyl ether (x3), and the organics were then washed with brine and dried with $MgSO_4$ and concentrated *in vacuo*. Pure material was *via* flash column chromatography (5% ether/hexanes), furnishing ketone **216** as a yellow oil (1.8 g, 79% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 7.89 (m, 2H), 7.51 – 7.45 (m, 1H), 7.44 – 7.35 (m, 2H), 6.98 – 6.89 (m, 2H), 6.82 (dt, *J* = 1.7, 0.9 Hz, 1H), 4.22 (d, *J* = 10.3 Hz, 1H), 2.27 (m, 7H), 1.85 – 1.78 (m, 1H), 1.69 – 1.61 (m, 3H), 1.38 – 1.28 (m, 2H), 1.22 – 1.09 (m, 2H), 1.00 – 0.92 (m, 1H), 0.89 – 0.80 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.0, 138.2, 138.0, 137.9, 132.8, 128.8, 128.63, 128.61, 126.8, 60.2, 41.3, 32.8, 31.0, 26.7, 26.4, 26.3, 21.5 cm^{-1}.

FT-IR (neat film NaCl): 2919, 2849, 1678, 1598, 1446, 1199, 727 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{22}H_{27}O$: 307.2062; Measured: 307.2058.



(*E*)-2-cyclohexyl-2-(3,5-dimethylphenyl)-1-phenylvinyl 4-methylbenzenesulfonate (202b)

To a flame-dried Schlenk flask was added 30% wt KH (3.88 g, 5 equiv, 29.0 mmol) then dissolved in THF (14 mL). In a separate flask, a solution of ketone **216** (1.78 g, 1.0 equiv, 5.81 mmol) in THF (7 mL) was prepared and added dropwise to the KH solution. The flask was then sealed and heated to 60 ºC for 7 hours. Then, the enolate solution was cooled to room temperature and Ts_2O (2.84 g, 1.5 equiv, 8.71 mmol) was added at once to the enolate solution with vigorous stirring (solution turns thick). Once the reaction was completed by TLC analysis (10% ether/hexanes), the reaction was quenched with water *very slowly* and extracted with ethyl acetate (x3). The combined organics were washed once with brine, dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica flash column chromatography (7% → 8% → 10% diethyl ether/hexanes) to yield vinyl tosylate **202b** as a white solid (490 mg, 18% yield). The olefin isomer is assigned to be *E* on the basis of NOESY NMR (observe NOE correlations between phenyl ring and 3,5-dimethylphenyl ring).

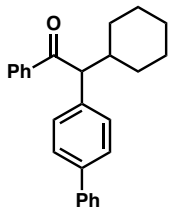
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.41 (m, 2H), 7.15 – 7.10 (m, 2H), 6.97 – 6.86 (m, 5H), 6.78 (dt, *J* = 1.6, 0.8 Hz, 1H), 6.57 (dt, *J* = 1.6, 0.8 Hz, 2H), 2.96 (tt, *J* = 11.9, 3.1 Hz, 1H), 2.37 (s, 3H), 2.18 (s, 6H), 1.72 – 1.57 (m, 5H), 1.28 (dtd, *J* = 13.5, 9.8, 3.6 Hz, 2H), 1.10 – 0.94 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.4, 142.3, 140.2, 136.9, 136.2, 134.5, 134.4, 129.6,

129.4, 128.6, 128.2, 128.1, 127.4, 127.2, 40.0, 31.0, 26.5, 25.9, 21.7, 21.4.

FT-IR (neat film NaCl): 2926, 2853, 1598, 1444, 1369, 1188, 1176, 1094, 1033, 1001, 968, 914, 824, 772, 695, 669 cm^{-1}.

HR-MS (ESI) m/z: [M+Na]+ Calculated for $C_{29}H_{32}NaO_3S$: 483.1964; Measured: 483.1973.



2-([1,1'-biphenyl]-4-yl)-2-cyclohexyl-1-phenylethan-1-one (217)

Following a slightly-modified reported procedure[31]: To a flame-dried Schlenk flask was added (IPr)Pd(acac)Cl (93.4 mg, 0.02 equiv, 0.15 mmol) and sodium *t*-pentoxide (1.22 g, 1.5 equiv, 11.1 mmol), and these solids were vac/backfilled with N_2 (x3). Anhydrous PhMe was then added (7.5 mL), followed by commercially available 4-bromo-1,1'-biphenyl (3.46 g, 2.0 equiv, 14.8 mmol) and ketone **214** (1.50 g, 1.0 equiv, 7.41 mmol). The Schlenk flask was then sealed and heated to 70 ºC. When the reaction reached completion (usually 12–14 hours later), the reaction was cooled to room temperature and diluted with water. The solution was extracted with diethyl ether (x3), and the organics were then washed with brine and dried with $MgSO_4$ and concentrated *in vacuo*. Pure material was obtained *via* flash column chromatography (5% ether/hexanes), furnishing ketone **217** as a white solid (1.8 g, 69% yield).

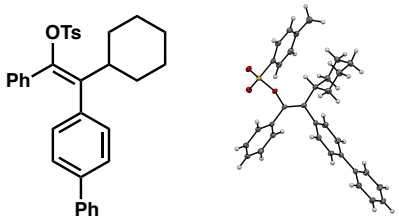
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 7.96 (m, 2H), 7.57 – 7.48 (m, 5H), 7.46 – 7.38 (m, 6H), 7.34 – 7.29 (m, 1H), 4.37 (d, *J* = 10.2 Hz, 1H), 2.39 – 2.28 (m, 1H), 1.86 (ddt, *J* =

12.4, 3.7, 1.9 Hz, 1H), 1.73 – 1.62 (m, 3H), 1.44 – 1.30 (m, 2H), 1.27 – 1.12 (m, 2H), 1.07 – 0.96 (m, 1H), 0.94 – 0.85 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.9, 140.8, 139.9, 137.9, 137.2, 133.0, 129.4, 128.9, 128.7, 128.6, 127.5, 127.3, 127.1, 59.8, 41.4, 32.8, 31.0, 26.7, 26.4, 26.3.

FT-IR (neat film NaCl): 3027, 2928, 2850, 1680, 1596, 1580, 1485, 1447, 1409, 1344, 1284, 1251, 1200, 1178, 1073, 1002, 957, 909, 844, 819, 760, 735, 692 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{26}H_{27}O$: 355.2062; Measured: 355.2059.



(*E*)-2-([1,1'-biphenyl]-4-yl)-2-cyclohexyl-1-phenylvinyl 4-methylbenzenesulfonate (202c)

To a flame-dried Schlenk flask was added 30% Wt KH (3.45 g, 5 equiv, 25.8 mmol) then dissolved in THF (12.6 mL). In a separate flask, a solution of ketone **217** (1.83 g, 1.0 equiv, 5.16 mmol) in THF (6 mL) was prepared and added dropwise to the KH solution. The flask was then sealed and heated to 40 ºC for 7 hours. Then, the enolate solution was cooled to room temperature and Ts_2O (2.53 g, 1.5 equiv, 7.74 mmol) was added at once to the enolate solution with vigorous stirring (solution turns thick). Once the reaction was completed by TLC analysis (10% ether/hexanes), the reaction was quenched with water *very slowly* and extracted with ethyl acetate (x3). The combined organics were washed once with brine, dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica flash column chromatography (8% diethyl ether/hexanes) to yield vinyl tosylate **202c** as a white solid

(412 mg, 16% yield). The olefin isomer is assigned to be *E* on the basis of NOESY NMR (observe NOE correlations between tosylate and piperidine protons). The olefin isomer was confirmed to be *E* on the basis of X-ray crystallographic analysis.

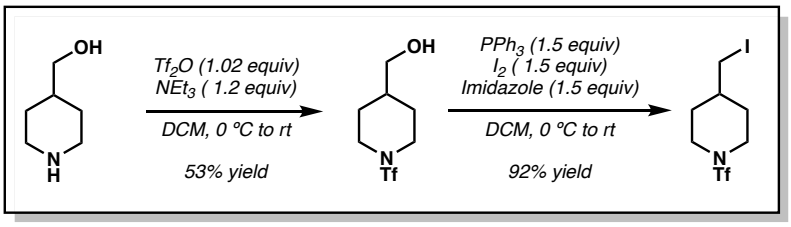
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.49 (m, 4H), 7.44 – 7.36 (m, 4H), 7.34 – 7.28 (m, 1H), 7.17 – 7.11 (m, 2H), 7.07 – 7.01 (m, 2H), 7.00 – 6.92 (m, 3H), 6.92 – 6.85 (m, 2H), 3.03 (tt, *J* = 12.1, 2.9 Hz, 1H), 2.37 (s, 3H), 1.77 – 1.66 (m, 4H), 1.64 – 1.57 (m, 1H), 1.32 (qt, *J* = 12.3, 2.9 Hz, 2H), 1.18 – 1.04 (m, 2H), 0.98 (dtd, *J* = 13.0, 9.6, 3.4 Hz, 1H).

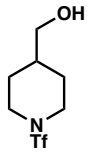
^{13}C NMR (101 MHz, $CDCl_3$) δ 145.0, 143.1, 141.0, 140.2, 139.9, 136.2, 134.83, 134.82, 131.3, 130.2, 129.9, 129.3, 128.6, 128.0, 127.9, 127.8, 127.4, 126.8, 40.6, 31.5, 26.9, 26.4, 22.1.

FT-IR (neat film NaCl): 3028, 2928, 2853, 1598, 1486, 1446, 1370, 1218, 1189, 1091, 1033, 1002, 959, 911, 858, 839, 812, 782, 733, 696, 666, 622 cm^{-1}.

HR-MS (ESI) m/z: [M+Na]+ Calculated for $C_{33}H_{32}NaO_3S$: 531.1964; Measured: 531.1969.

Representative scheme for the synthesis of N-Tf piperidinyl iodide:





(1-((trifluoromethyl)sulfonyl)piperidin-4-yl)methanol (218)

To a flame-dried flask with a magnetic stir bar was added commercially available piperidin-4-ylmethanol (9.80 g, 1.0 equiv, 85.0 mmol) followed by 140 mL dry DCM and 14.2 mL of freshly distilled (over CaH_2) triethylamine (10.33 g, 1.2 equiv, 102.1 mmol). The solution was cooled to 0 ºC and allowed to stir for 20 minutes at this temperature. Then, freshly dried and distilled (over P_2O_5) Tf_2O (24.48 mmol, 1.02 equiv, 86.79 mmol) was added dropwise very slowly over the course of ~20 minutes. The reaction was allowed to stir at 0 ºC for 2 hours, then warmed to room temperature and allowed to stir overnight. The next morning, the reaction was cooled again to 0 ºC and quenched with water and extracted with DCM (x3). The combined organics were dried over Na_2SO_4, filtered, then concentrated *in vacuo*. The crude material was purified *via* silica flash column chromatography (20% diethyl ether in DCM, product stains with $KMnO_4$ TLC stain) to yield alcohol **218** as a white solid (11.2 g, 53% yield).

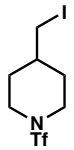
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99 (d, J = 13.1 Hz, 2H), 3.55 (d, J = 6.3 Hz, 2H), 3.04 (t, J = 12.7 Hz, 2H), 1.95 – 1.82 (m, 2H), 1.80 – 1.58 (m, 1H), 1.45 (br s, 1H), 1.41 – 1.27 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 120.2 (q, J = 323 Hz), 66.9, 46.8, 37.8, 28.6.

^{19}F NMR (376 MHz, $CDCl_3$) δ -75.2 (br s).

FT-IR (neat film NaCl): 3333, 2927, 1447, 1385, 1227, 1184, 1150, 1124, 1049, 980, 939, 762, 708, 683 cm^{-1}.

HR-MS (FD) m/z: [M•]+ Calculated for $C_7H_{12}F_3NO_3S$: 247.0490; Measured: 247.0481.



4-(iodomethyl)-1-((trifluoromethyl)sulfonyl)piperidine (219)

To a flame-dried flask with a magnetic stir bar was added PPh_3 (18.1 g, 1.5 equiv, 69.2 mmol) and imidazole (4.7 g, 1.5 equiv, 69.2 mmol). The solids were dissolved in 145 mL dry DCM then cooled to 0 ºC. After stirring at this temperature for 20 minutes, solid I_2 (17.6g, 1.5 equiv, 69.2 mmol) was added in three portions and allowed to stir for another 30 minutes at 0 ºC under N_2. Then, a solution of alcohol **218** (11.4 g, 1.0 equiv, 46.1 mmol) in 30 mL dry DCM was added dropwise and the reaction was allowed to warm up to room temperature overnight. The next morning (SM consumed by TLC) saturated aqueous $Na_2S_2O_3$ was added and then subsequently extracted with DCM (x3). The combined organics were dried over Na_2SO_4, filtered, concentrated *in vacuo*, then purified *via* silica flash column chromatography (20% diethyl ether in hexanes) to yield pure iodide **219** as a white solid (15.2 g, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (dt, *J* = 13.3, 2.5 Hz, 2H), 3.11 (d, *J* = 6.5 Hz, 2H), 3.01 (t, *J* = 12.8 Hz, 2H), 2.30 – 1.81 (m, 2H), 1.63 (m, 1H), 1.39 – 1.24 (m, 2H).

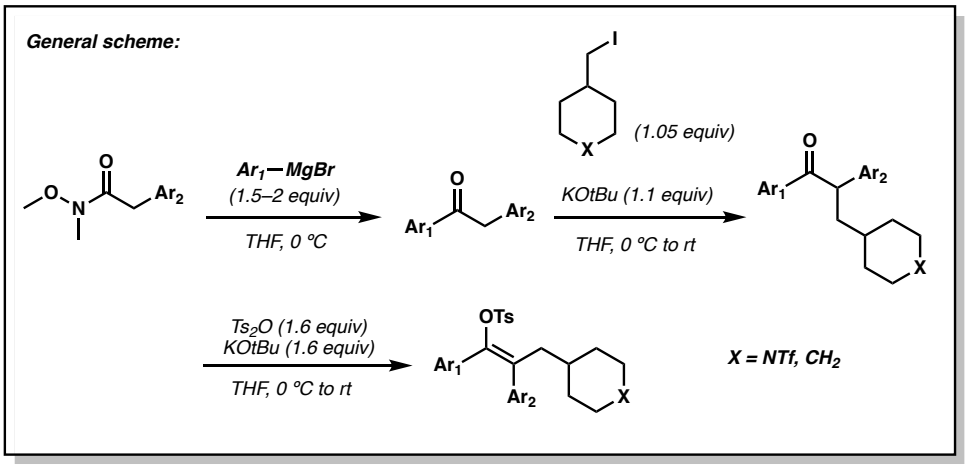
^{13}C NMR (101 MHz, $CDCl_3$) δ 120.0 (q, *J* = 323.4 Hz), 46.4, 37.4, 32.2, 11.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ -75.3 (br s).

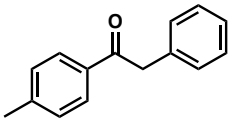
FT-IR (neat film NaCl): 2946, 2881, 1466, 1447, 1391, 1355, 1296, 1254, 1228, 1190, 1143, 1062, 1039, 993, 977, 945, 846, 810, 764, 709, 683, 668, 620 cm^{-1}.

HR-MS (FD) m/z: [M•]+ Calculated for $C_7H_{11}F_3INO_2S$: 356.9507; Measured: 356.9493.

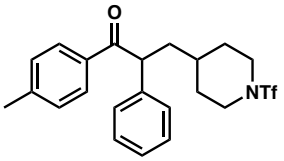
Representative scheme for the synthesis of N-Tf piperidinyl vinyl tosylate substrates:



The general procedure outlined above was used to prepare N-Tf piperidinyl vinyl tosylate substrates from the corresponding aryl acetic acid-derived Weinreb amides, which were prepared according to published procedures.[32] The procedure for synthesis of aryl acetophenones was adopted from Schindler *et al*.[33] The tosylation step generates the *E* isomer shown as the major isomer, but some *Z* isomer is also produced, which is typically more polar in R_f and could be separated out via column chromatography. While both the *Z* and *E* isomer of the vinyl tosylate give similar results in C–H insertion reactions (activity and enantioselectivity), only the *E* isomer was used for experiments unless otherwise noted. *If the vinyl tosylate is impure after column chromatography, pure material could be obtained via recrystallization from hexanes/ethyl acetate or hexanes/diethyl ether.



2-phenyl-1-(*p*-tolyl)ethan-1-one (220) was prepared according to literature procedures and matched the NMR data in the literature.[34]



2-phenyl-1-(*p*-tolyl)-3-(1-((trifluoromethyl)sulfonyl)piperidin-4-yl)propan-1-one (221)

To a flamed-dried flask was added KOtBu (293 mg, 1.1 equiv, 2.6 mmol). This flask was evacuated under vacuum and backfilled with nitrogen three times. To this was added THF (8 mL), and the flask was cooled to 0 ºC. To this flask was added ketone **220** (0.50 g, 1.0 equiv, 2.4 mmol) in THF (4 mL), and the solution was stirred at 0 ºC for 20 minutes. To this was added a solution of iodide **219** (892 mg, 1.05 equiv, 2.50 mmol) in THF (4 mL). The reaction flask was allowed to warm up to room temperature overnight and quenched by addition of saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with ethyl acetate (3x 15 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica flash column chromatography (5% ethyl acetate in hexanes) to yield ketone **221** as a white solid (788 mg, 75% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 8.1 Hz, 2H), 7.28 – 7.23 (m, 5H), 7.17 (d, J = 8.1 Hz, 2H), 4.63 (t, J = 7.5 Hz, 1H), 4.09 – 3.66 (m, 2H), 2.90 (q, J = 13.0 Hz, 2H), 2.29 – 2.04 (m, 3H), 1.98 – 1.63 (m, 1H), 1.50 – 1.13 (m, 3H).

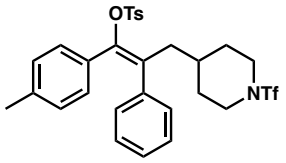
^{13}C NMR (101 MHz, $CDCl_3$) δ 198.6, 144.1, 139.3, 133.9, 129.3, 129.0, 128.7, 127.9, 127.2, 120.0 (q, J = 323.7 Hz), 50.0, 46.7, 40.08, 32.82, 31.91, 21.57.

^{19}F NMR (282 MHz, $CDCl_3$) δ -75.2.

FT-IR (neat film NaCl): 2919, 1675, 1604, 1460, 1387, 1182, 1149, 1118, 1047, 949, 937, 706 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{22}H_{25}F_3NO_3S$: 440.1507; Measured:

440.1509.



2-phenyl-1-(*p*-tolyl)-3-(1-((trifluoromethyl)sulfonyl)piperidin-4-yl)prop-1-en-1-yl 4-methylbenzenesulfonate (212a)

To a flame-dried flask was added KOtBu (666 mg, 1.5 equiv, 5.94 mmol) and THF (15 mL). This solution was cooled to 0 ºC and ketone **221** (1.74 g, 1.0 equiv, 3.9 mmol) was added dropwise as a solution in THF (10 mL). This solution was stirred at 0 ºC for 1 hour. To this was added *p*-toluenesulfonic anhydride (1.94 g, 1.5 equiv, 5.94 mmol) as a fine suspension in THF (15 mL). This solution was allowed to warm to room temperature and stirred for 1 hour. The reaction was diluted with ethyl acetate (30 mL) and 1M aqueous NaOH (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by flash column chromatography (1% → 20% ether in hexanes). The new spot was collected (lower in R_f than starting ketone), which correspond to the *E* vinyl tosylate as **212a** (942 mg, 40% yield, white solid). The olefin isomer is assigned to be *E* on the basis of NOESY NMR (observe NOE correlations between tosylate and piperidine fragments). Consistent with this assignment, the chemical shift of the allylic methylene protons (2.73 ppm) is congruent to similarly reported *E* diaryl vinyl tosylates (typically ~2.7 ppm for allylic methylene), which are distinct from the reported *Z* isomer chemical shift (typically ~2.3 ppm for allylic methylene of corresponding *Z* vinyl tosylate).[35]

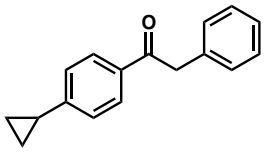
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.3 Hz, 2H), 7.21 – 7.14 (m, 3H), 7.09 (d, *J* = 8.1 Hz, 1H), 7.02 (dd, *J* = 6.6, 2.9 Hz, 2H), 6.80 – 6.62 (m, 2H), 3.84 (d, *J* = 13.0 Hz, 2H), 2.89 (s, 1H), 2.69 (d, *J* = 6.3 Hz, 2H), 2.37 (s, 3H), 2.18 (s, 3H), 1.71 (d, *J* = 11.8 Hz, 2H), 1.44 – 1.17 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9, 144.4, 138.2, 137.9, 134.3, 131.6, 130.2, 129.8, 129.2, 129.2, 128.4, 128.1, 127.9, 127.3, 120.1 (q, *J* = 323.3 Hz), 46.6, 38.7, 33.0, 31.4, 21.5, 21.2.

^{19}F NMR (282 MHz, $CDCl_3$) δ -75.3 (br s).

FT-IR (neat film NaCl): 2927, 1598, 1386, 1226, 1188, 1150, 1049, 971, 941, 849 cm^{-1}.

HR-MS (EI-MS) m/z: [M+K]+ Calculated for $C_{29}H_{30}F_3NO_5S_2K$: 632.1155; Measured: 632.1166.



1-(4-cyclopropylphenyl)-2-phenylethan-1-one (222)

Magnesium turnings (546 mg, 1.75 equiv, 22.5 mmol) were flame-dried under high vacuum in a round bottom flask (x3) then suspended in dry THF (64 mL). Commercially available 1-bromo-4-cyclopropylbenzene (5.06 g, 2.0 equiv, 25.7 mmol, 3.4 mL) was added followed by a small grain of I_2. The solution was allowed to stir with gentle heating *via* a heat gun until the purple-brown color of the I_2 disappears. The suspension was then stirred until all the magnesium turnings are visibly consumed. At this point, the reaction was cooled to 0 ºC, and then a solution of *N*-methoxy-*N*-methyl-2-phenylacetamide (2.30 g, 1.0 equiv, 12.80 mmol) in 6.4 mL THF was added dropwise. The reaction was monitored

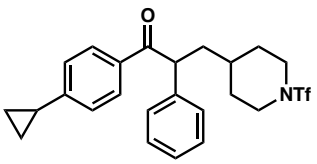
closely by TLC to determine starting material consumption (usually 5–20 minutes), then quenched with 30 mL saturated aqueous ammonium chloride while at 0 ºC. The reaction was extracted with diethyl ether (x3), then the combined organics were washed with brine, dried over $MgSO_4$, filtered through a short pad of silica (wash through with diethyl ether), and concentrated *in vacuo*. Pure material was obtained *via* silica flash column chromatography (7.5% ether/hexanes), furnishing ketone **222** as a white solid (2.6 g, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.84 (m, 2H), 7.31 – 7.25 (m, 2H), 7.25 – 7.17 (m, 3H), 7.11 – 7.05 (m, 2H), 4.21 (s, 2H), 1.90 (ddd, J = 8.4, 5.1, 3.4 Hz, 1H), 1.06 – 0.98 (m, 2H), 0.78 – 0.69 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.2, 150.6, 135.0, 134.1, 129.5, 129.0, 128.8, 126.9, 125.7, 45.5, 15.9, 10.5.

FT-IR (neat film NaCl): 1676, 1604, 1459, 1411, 1328, 1044, 812, 713 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{17}H_{17}O$: 237.1274; Measured: 237.1275.



1-(4-cyclopropylphenyl)-2-phenyl-3-(1-((trifluoromethyl)sulfonyl)piperidin-4-yl)propan-1-one (223)

To a flamed-dried flask was added KOtBu (1.16 g, 1.1 equiv, 10.36 mmol). This flask was evacuated under vacuum and backfilled with nitrogen three times. To this was added THF (24 mL), and the flask was cooled to 0 ºC. To this flask was added ketone **222** (2.22 g, 1.0 equiv, 9.4 mmol) in THF (20.5 mL), and the solution was stirred at 0 ºC for 20 minutes. To this was added a solution of iodide **219** (3.53 g, 1.05 equiv, 9.89 mmol) in THF (16

mL). The reaction flask was allowed to warm up to room temperature overnight, and quenched by addition of saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with ethyl acetate (3x 15 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica flash column chromatography (15 → 20% diethyl ether in hexanes) to yield ketone **223** as a white solid (2.6 g, 59% yield).

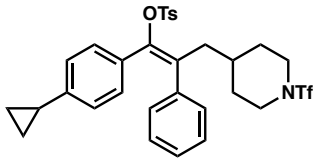
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.5 Hz, 2H), 7.32 – 7.23 (m, 4H), 7.19 (tddd, *J* = 5.6, 4.9, 3.3, 2.6 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 2H), 4.62 (dd, *J* = 8.1, 6.7 Hz, 1H), 3.87 (tt, *J* = 12.8, 2.1 Hz, 2H), 2.90 (dt, *J* = 22.2, 12.7 Hz, 2H), 2.19 (ddd, *J* = 14.4, 8.1, 6.5 Hz, 1H), 1.94 – 1.81 (m, 2H), 1.81 – 1.65 (m, 2H), 1.48 – 1.23 (m, 3H), 1.07 – 0.96 (m, 2H), 0.71 (qd, *J* = 4.8, 2.6 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.6, 150.7, 139.6, 133.9, 129.2, 129.0, 128.1, 127.4, 125.7, 120.2 (q, *J* = 323.4 Hz), 77.5, 77.2, 76.8, 50.2, 46.90, 46.88, 40.3, 33.0, 32.1, 15.8, 10.57, 10.55.

^{19}F NMR (376 MHz, $CDCl_3$) δ -75.2.

FT-IR (neat film NaCl): 3007, 2936, 1674, 1604, 1566, 1493, 1453, 1415, 1386, 1273, 1253, 1226, 1186, 1146, 1117, 1049, 998, 949, 910, 823, 728, 709, 610 cm^{-1}.

HR-MS (ESI) m/z: [M+Na]+ Calculated for $C_{24}H_{26}F_3NNaO_3S$: 488.1478; Measured: 488.1471.



(*E*)-1-(4-cyclopropylphenyl)-2-phenyl-3-(1-((trifluoromethyl)sulfonyl)piperidin-4-yl)prop-1-en-1-yl 4-methylbenzenesulfonate (212b)

To a flame-dried flask was added ketone **223** (1.00 g, 1.0 equiv, 2.15 mmol) and dry THF (2.60 mL). A 1.0 M solution of LiOtBu in THF (3.2 mL) was added dropwise and stirred at room temperature for 30 minutes. Then, *p*-toluenesulfonic anhydride (1.05 g, 1.5 equiv, 3.22 mmol) in THF (5.6 mL) was added dropwise to the enolate solution with vigorous stirring, and then the solution was allowed to warm to room temperature (solution turns thick). This solution was then stirred for 1 hour. The reaction was quenched with $NaHCO_3$ (10 mL) and extracted with diethyl ether (3 x 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica flash chromatography (20% diethyl ether in hexanes) to give vinyl tosylate **212b** (300 mg, 23% yield). The olefin isomer is assigned to be *E* on the basis of NOESY NMR (observe NOE correlations between tosylate and piperidine fragments). Consistent with this assignment, the chemical shift of the allylic methylene protons (2.72 ppm in $CDCl_3$) is congruent to similarly reported *E* diaryl vinyl tosylates (typically ~2.7 ppm for allylic methylene in $CDCl_3$), which are distinct from the reported *Z* isomer chemical shift (typically ~2.3 ppm for allylic methylene of corresponding *Z* vinyl tosylate in $CDCl_3$).[35]

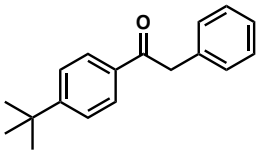
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.36 (m, 2H), 7.22 – 7.13 (m, 3H), 7.13 – 6.99 (m, 4H), 6.70 (d, *J* = 8.4 Hz, 2H), 6.54 (d, *J* = 8.3 Hz, 2H), 3.85 (dd, *J* = 13.3, 4.0 Hz, 2H), 2.89 (s, 2H), 2.72 (d, *J* = 6.0 Hz, 2H), 2.36 (s, 3H), 1.71 (tdd, *J* = 8.4, 5.3, 2.8 Hz, 3H), 1.38 (dt, *J* = 11.9, 6.1 Hz, 3H), 0.95 – 0.85 (m, 2H), 0.53 (dt, *J* = 6.6, 4.6 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.1, 144.4, 144.3, 138.4, 134.5, 131.7, 130.3, 129.9, 129.3, 129.3, 128.5, 128.0, 127.4, 124.6, 123.9 (*J* = 323.9 HZ), 46.7, 38.9, 33.2, 31.5, 31.5, 21.6, 15.2, 9.7.

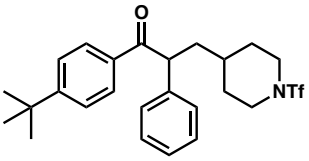
^{19}F NMR (376 MHz, $CDCl_3$) δ -75.2.

FT-IR (neat film NaCl): 2924, 1598, 1444, 1387, 1226, 1188, 1177, 1149, 1116, 1049, 968, 941, 848, 830, 812, 777, 757, 707 cm^{-1}.

HR-MS (ESI) m/z: [M+Na]+ Calculated for $C_{31}H_{32}F_3NNaO_5S_2$: 642.1566; Measured: 642.1586.



1-(4-(*tert*-butyl)phenyl)-2-phenylethan-1-one (224) was prepared according to literature procedures and matched the NMR data in the literature.[34]



1-(4-(*tert*-butyl)phenyl)-2-phenyl-3-(1-((trifluoromethyl)sulfonyl)piperidin-4-yl)propan-1-one (225)

To a flamed-dried flask was added KOtBu (734 mg, 1.1 equiv, 6.54 mmol). This flask was evacuated under vacuum and backfilled with nitrogen three times. To this was added THF (15 mL), and the flask was cooled to 0 ºC. To this flask was added ketone **224** (1.50 g, 1.0 equiv, 5.94 mmol) in THF (13 mL), and the solution was stirred at 0 ºC for 20 minutes. To this was added a solution of iodide **219** (2.23 g, 1.05 equiv, 6.24 mmol) in THF (10 mL). The reaction flask was allowed to warm up to room temperature overnight, and quenched by addition of saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with ethyl acetate (3x 15 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified

by silica flash column chromatography (10% diethyl ether in hexanes) to yield ketone **225** as a white solid (2.0 g, 70% yield).

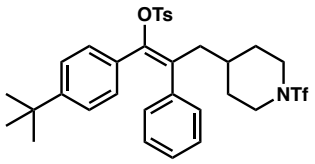
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.88 (m, 2H), 7.44 – 7.39 (m, 2H), 7.30 (d, J = 4.9 Hz, 4H), 7.25 – 7.19 (m, 1H), 4.66 (dd, J = 8.2, 6.7 Hz, 1H), 3.89 (tdt, J = 13.0, 4.4, 2.4 Hz, 2H), 3.04 – 2.80 (m, 2H), 2.22 (ddd, J = 14.4, 8.2, 6.5 Hz, 1H), 1.89 (dp, J = 13.2, 2.7 Hz, 1H), 1.81 – 1.71 (m, 2H), 1.47 – 1.30 (m, 3H), 1.30 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.7, 157.1, 139.5, 134.0, 129.3, 128.8, 128.2, 127.4, 125.8, 120.2 (q, J = 323.9 Hz), 77.5, 77.2, 76.8, 50.3, 46.91, 46.88, 40.4, 35.2, 33.0, 32.08, 32.05, 31.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ -75.8.

FT-IR (neat film NaCl): 2963, 2870, 1676, 1603, 1387, 1268, 1226, 1186, 1147, 1117, 1051, 949, 709 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{25}H_{31}F_3NO_3S$: 482.1971; Measured: 482.1972.



(*E*)-1-(4-(*tert*-butyl)phenyl)-2-phenyl-3-(1-((trifluoromethyl)sulfonyl)piperidin-4-yl)prop-1-en-1-yl 4-methylbenzenesulfonate (212c)

To a flame-dried flask was added KOtBu (708 mg, 1.6 equiv, 6.31 mmol) and THF (9 mL). This solution was cooled to 0 ºC and ketone **225** (1.90 g, 1.0 equiv, 3.95 mmol) was added dropwise as a solution in THF (14 mL). This solution was stirred at 0 ºC for 2 hours. To this was quickly added solid toluenesulfonic anhydride (2.06 g, 1.6 equiv, 6.31 mmol) with

vigorous stirring, and then the solution was allowed to warm to room temperature (solution turns thick). After 1.5 hours, the reaction was diluted with ethyl acetate (15 mL) and water (15 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica flash column chromatography (15% diethyl ether in hexanes) to give vinyl tosylate **212c** (1.0 g, 40% yield). The olefin isomer is assigned to be *E* on the basis of NOESY NMR (observe NOE correlations between tosylate and piperidine fragments). Consistent with this assignment, the chemical shift of the allylic methylene protons (2.77 ppm in $CDCl_3$) is congruent to similarly reported *E* diaryl vinyl tosylates (typically ~2.7 ppm for allylic methylene in $CDCl_3$), which are distinct from the reported *Z* isomer chemical shift (typically ~2.3 ppm for allylic methylene of corresponding *Z* vinyl tosylate in $CDCl_3$).[35]

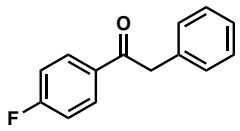
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.4 Hz, 2H), 7.21 – 7.15 (m, 3H), 7.06 – 6.98 (m, 4H), 6.86 – 6.81 (m, 2H), 6.76 – 6.69 (m, 2H), 3.87 (dd, *J* = 13.3, 3.9 Hz, 2H), 2.90 (t, *J* = 10.8 Hz, 2H), 2.77 (d, *J* = 6.2 Hz, 2H), 2.31 (s, 3H), 1.79 – 1.68 (m, 2H), 1.46 – 1.32 (m, 3H), 1.17 (s, 9H).

^{13}C NMR = (101 MHz, $CDCl_3$) δ 151.1, 145.1, 144.2, 138.4, 134.6, 132.0, 130.2, 129.7, 129.4, 129.3, 128.5, 128.1, 127.4, 124.40, 120.2 (app q, *J* = 323.5 Hz), 46.8, 39.0, 34.6, 33.30, 33.28, 33.26, 33.2, 31.6, 31.3, 21.7.

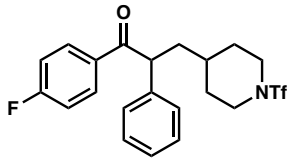
^{19}F NMR (282 MHz, $CDCl_3$) δ -75.3.

FT-IR (neat film NaCl): 2960, 1598, 1444, 1389, 1227, 1177, 1150, 1116, 1065, 1049, 971, 942, 913, 852, 839, 812, 779, 760, 732, 707 cm^{-1}.

HR-MS (ESI) m/z: [M+K]+ Calculated for $C_{32}H_{36}F_3KNO_5S_2$: 674.1619; Measured: 674.1622.



1-(4-fluorophenyl)-2-phenylethan-1-one (226) was prepared according to literature procedures and matched the NMR data in the literature.[36]



1-(4-fluorophenyl)-2-phenyl-3-(1-((trifluoromethyl)sulfonyl)piperidin-4-yl)propan-1-one (227)

To a flamed-dried flask was added KOtBu (576 mg, 1.1 equiv, 5.13 mmol). This flask was evacuated under vacuum and backfilled with nitrogen three times. To this was added THF (12 mL), and the flask was cooled to 0 ºC. To this flask was added ketone **226** (1.00 g, 1.0 equiv, 4.67 mmol) in THF (10 mL), and the solution was stirred at 0 ºC for 20 minutes. To this was added a solution of iodide **219** (1.75 g, 1.05 equiv, 4.90 mmol) in THF (8 mL). The reaction flask was allowed to warm up to room temperature overnight, and quenched by addition of saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with ethyl acetate (3x 15 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica flash column chromatography (10% diethyl ether in hexanes) to yield ketone **227** as a white solid (1.45 g, 70% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.88 (m, 2H), 7.32 – 7.19 (m, 5H), 7.11 – 6.98 (m, 2H), 4.58 (t, *J* = 7.4 Hz, 1H), 3.89 (ddt, *J* = 15.1, 12.8, 2.1 Hz, 2H), 2.92 (d, *J* = 15.3 Hz,

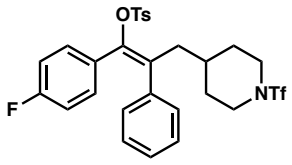
2H), 2.18 (ddd, *J* = 14.4, 7.8, 6.6 Hz, 1H), 1.88 (dt, *J* = 12.8, 2.5 Hz, 1H), 1.79 (dt, *J* = 13.7, 6.7 Hz, 1H), 1.71 (dt, *J* = 12.9, 2.6 Hz, 1H), 1.44 – 1.23 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.6, 165.8 d, *J* = 255.5 Hz), 139.1, 132.9 (d, J = 3.0 Hz), 131.5 (d, *J* = 9.2 Hz), 129.4, 128.1, 127.6, 120.2 (q, *J* = 323.9 Hz), 116.0, 115.8, 77.5, 77.2, 76.8, 50.5, 46.9, 40.2, 32.9, 32.1, 32.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ -75.8, -104.8.

FT-IR (neat film NaCl): 2929, 1680, 1597, 1505, 1448, 1386, 1275, 1226, 1187, 1155, 1118, 1052, 948, 741, 709 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{21}H_{22}F_4NO_3S$: 444.1251; Measured: 444.1252.



(*E*)-1-(4-fluorophenyl)-2-phenyl-3-(1-((trifluoromethyl)sulfonyl)piperidin-4-yl)prop-1-en-1-yl 4-methylbenzenesulfonate (212d)

To a flame-dried flask was added KOtBu (555 mg, 1.6 equiv, 4.94 mmol) and THF (7 mL). This solution was cooled to 0 ºC and ketone **227** (1.37 g, 1.0 equiv, 3.09 mmol) was added dropwise as a solution in THF (11 mL). This solution was stirred at 0 ºC for 2 h. To this was quickly added solid toluenesulfonic anhydride (1.61 g, 1.6 equiv, 4.94 mmol). This solution was allowed to warm to room temperature and stirred for 1.5 hours. The reaction was diluted with ethyl acetate (15 mL) and water (15 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica flash column chromatography (25%

diethyl ether in hexanes) to give vinyl tosylate **212d** (700 mg, 38% yield) as a white solid. The olefin isomer is assigned to be *E* on the basis of NOESY NMR (observe NOE correlations between tosylate and piperidine fragment). Consistent with this assignment, the chemical shift of the allylic methylene protons (2.71 ppm in $CDCl_3$) is congruent to similarly reported *E* diaryl vinyl tosylates (typically ~2.7 ppm for allylic methylene in $CDCl_3$), which are distinct from the reported *Z* isomer chemical shift (typically ~2.3 ppm for allylic methylene of corresponding *Z* vinyl tosylate in $CDCl_3$).[35]

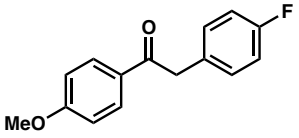
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.36 (m, 2H), 7.24 – 7.16 (m, 3H), 7.13 (d, *J* = 8.1 Hz, 2H), 7.04 – 6.96 (m, 2H), 6.89 – 6.78 (m, 2H), 6.66 – 6.54 (m, 2H), 3.93 – 3.76 (m, 2H), 2.89 (t, *J* = 10.8 Hz, 2H), 2.71 (d, *J* = 6.0 Hz, 2H), 2.38 (s, 3H), 1.72 (dd, *J* = 12.8, 2.8 Hz, 2H), 1.46 – 1.28 (m, 3H).

^{13}C NMR = (101 MHz, $CDCl_3$) δ 162.2 (d, *J* = 249.3 Hz) 145.0, 143.9, 138.0, 134.4, 132.8, 131.9 (d, *J* = 8.4 Hz), 129.8 (d, *J* = 3.5 Hz),129.5, 129.3, 128.7, 128.0, 127.7, 120.2 (q, *J* = 323.5 Hz), 114.8, 114.6, 46.7, 38.9, 33.2, 31.6, 21.7.

^{19}F NMR (282 MHz, $CDCl_3$) δ -75.3, -112.3.

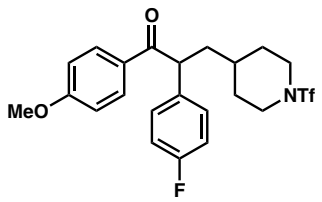
FT-IR (neat film NaCl): 3052, 2927, 2874, 1649, 1600, 1508, 1493, 1445, 1385, 1334, 1306, 1276, 1227, 1189, 1178, 1150, 1116, 1080, 1065, 1049, 975, 942, 911, 852, 814, 776, 760, 735, 708, 673 cm^{-1}.

HR-MS (ESI) m/z: [M+Na]+ Calculated for $C_{28}H_{27}F_4NNaO_5S_2$: 620.1159; Measured: 620.1170.



2-(4-fluorophenyl)-1-(4-methoxyphenyl)ethan-1-one (228)

Prepared according to literature procedures and matched the NMR data in the literature.[37]



2-(4-fluorophenyl)-1-(4-methoxyphenyl)-3-(1-((trifluoromethyl)sulfonyl)piperidin-4-yl)propan-1-one (229)

To a flamed-dried flask was added KOtBu (884 mg, 1.1 equiv, 7.88 mmol). This flask was evacuated under vacuum and backfilled with nitrogen three times. To this was added THF (18 mL), and the flask was cooled to 0 ºC. To this flask was added ketone **228** (1.750 g, 1 equiv, 7.164 mmol) in THF (16 mL), and the solution was stirred at 0 ºC for 20 minutes. To this was added a solution of iodide **219** (2.69 g, 1.05 equiv, 7.52 mmol). The reaction flask was allowed to warm up to room temperature overnight, and quenched by addition of saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with ethyl acetate (3x 15 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica flash column chromatography (30% diethyl ether in hexanes) to yield ketone **229** as a white solid (2.00 g, 59% yield).

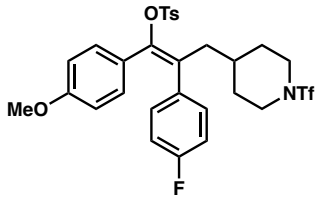
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.90 (m, 2H), 7.30 – 7.23 (m, 2H), 7.04 – 6.95 (m, 2H), 6.93 – 6.85 (m, 2H), 4.63 (dd, J = 8.1, 6.8 Hz, 1H), 3.96 – 3.86 (m, 2H), 3.84 (s, 3H), 2.93 (q, J = 13.7 Hz, 2H), 2.24 – 2.16 (m, 1H), 1.88 (dt, J = 12.4, 2.6 Hz, 1H), 1.80 – 1.71 (m, 2H), 1.44 – 1.26 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.6, 163.8, 162.0 (d, *J* = 246.2 Hz), 135.4 (d, *J* = 3.3 Hz), 131.0, 129.6 (d, *J* = 8.0 Hz), 129.3, 120.2 (q, *J* = 323.5 Hz), 116.2, 116.0, 114.0, 55.6, 49.0, 46.9, 40.4, 33.0, 32.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ -75.2, -115. 2.

FT-IR (neat film NaCl): 2941, 1672, 1600, 1575, 1508, 1460, 1421, 1385, 1313, 1252, 1226, 1172, 1151, 1117, 1049, 1030, 949, 836, 709 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{22}H_{24}F_4NO_4S$: 474.1357; Measured: 474.1356.



(*E*)-2-(4-fluorophenyl)-1-(4-methoxyphenyl)-3-(1-((trifluoromethyl)sulfonyl)piperidin-4-yl)prop-1-en-1-yl 4-methylbenzenesulfonate (212e)

To a flame-dried flask was added KOtBu (728 mg, 1.6 equiv, 6.49 mmol) and THF (10.6 mL). This solution was cooled to 0 ºC and ketone **229** (1.92 g, 1.0 equiv, 4.06 mmol) was added dropwise as a solution in THF (10.5 mL). This solution was stirred at 0 ºC for 2 hours. To this was quickly added solid toluenesulfonic anhydride (2.12 g, 1.6 equiv, 6.49 mmol). This solution was allowed to warm to room temperature and stirred for 1.5 hours. The reaction was diluted with ethyl acetate (15 mL) and water (15 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica flash column

chromatography (25% ether in hexanes) to give vinyl tosylate **212e** (1.0 g, 40% yield). The olefin isomer is assigned to be *E* on the basis of NOESY NMR (observe NOE correlations between tosylate and piperidine fragments). Consistent with this assignment, the chemical shift of the allylic methylene protons (2.68 ppm in $CDCl_3$) is congruent to similarly reported *E* diaryl vinyl tosylates (typically ~2.7 ppm for allylic methylene in $CDCl_3$), which are distinct from the reported *Z* isomer chemical shift (typically ~2.3 ppm for allylic methylene of corresponding *Z* vinyl tosylate in $CDCl_3$).[35]

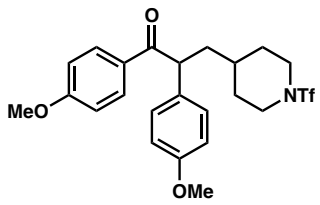
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.13 – 7.07 (m, 2H), 7.02 – 6.96 (m, 2H), 6.91 – 6.84 (m, 2H), 6.79 – 6.73 (m, 2H), 6.47 – 6.40 (m, 2H), 3.85 (dt, *J* = 12.2, 2.9 Hz, 2H), 3.69 (s, 3H), 2.90 (t, *J* = 12.0 Hz, 2H), 2.68 (d, *J* = 6.2 Hz, 2H), 2.37 (s, 3H), 1.74 – 1.66 (m, 2H), 1.37 (dt, *J* = 12.2, 6.1 Hz, 3H).

^{13}C NMR = (101 MHz, $CDCl_3$) δ 161.9 (d, *J* = 247.4 Hz), 159.4, 145.2, 144.6, 134.5, 134.4 (d, *J* = 3.4 Hz), 131.4, 131.1 (d, *J* = 7.8 Hz), 130.2, 129.4, 128.0, 125.7, 120.2 (app q, *J* = 323.5 Hz), 115.8, 115.6, 113.2, 55.3, 46.7, 38.8, 33.3, 31.6, 21.7.

^{19}F NMR (282 MHz, $CDCl_3$) δ -75.3, -114.2

FT-IR (neat film NaCl): 2941, 1604, 1509, 1464, 1446, 1385, 1295, 1251, 1226, 1189, 1177, 1151, 1115, 1095, 1067, 1049, 972, 943, 855, 839, 815, 784, 728, 709 cm $^{-1}$.

HR-MS (ESI) m/z: [M+Na]+ Calculated for $C_{29}H_{29}F_4NNaO_6S_2$: 650.1265; Measured: 650.1279.



1,2-bis(4-methoxyphenyl)-3-(1-((trifluoromethyl)sulfonyl)piperidin-4-yl)propan-1-one (230)

To a flamed dried flask was added KOtBu (674 mg, 1.1 equiv, 6.01 mmol). This flask was evacuated under vacuum and backfilled with nitrogen three times. To this was added THF (14 mL), and the flask was cooled to 0 ºC. To this flask was added commercially available 1,2-bis(4-methoxyphenyl)ethan-1-one (1.40 g, 1.0 equiv, 5.46 mmol) in THF (12 mL), and the solution was stirred at 0 ºC for 20 minutes. To this was added a solution of iodide **219** (2.05 g, 1.05 equiv, 6.24 mmol). The reaction flask was allowed to warm up to room temperature overnight, and quenched by addition of saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with ethyl acetate (3x 15 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica flash column chromatography (20% diethyl ether in hexanes) to yield ketone **230** as a white solid (1.80 g, 68% yield).

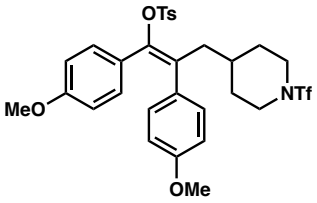
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.92 (m, 2H), 7.22 – 7.16 (m, 2H), 6.90 – 6.85 (m, 2H), 6.85 – 6.80 (m, 2H), 4.57 (t, *J* = 7.4 Hz, 1H), 3.90 (ddd, *J* = 16.8, 8.1, 6.1 Hz, 2H), 3.82 (s, 3H), 3.75 (s, 3H), 2.93 (q, *J* = 13.8 Hz, 2H), 2.16 (ddd, *J* = 14.3, 7.9, 6.6 Hz, 1H), 1.88 (dt, *J* = 13.2, 2.7 Hz, 1H), 1.79 – 1.69 (m, 2H), 1.45 – 1.26 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.9, 163.6, 158.8, 131.6, 131.1, 129.6, 129.1, 120.2 (q, *J* = 323.1 Hz), 114.6, 113.9, 55.6, 55.3, 49.1, 46.9, 40.2, 32.9, 32.1, 32.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ -75.2.

FT-IR (neat film NaCl): 2937, 1670, 1600, 1574, 1510, 1463, 1420, 1385, 1310, 1251, 1182, 1147, 1119, 1031, 949, 830, 709 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{23}H_{27}F_3NO_5S$: 486.1557; Measured: 486.1567.



(*E*)-1,2-bis(4-methoxyphenyl)-3-(1-((trifluoromethyl)sulfonyl)piperidin-4-yl)prop-1-en-1-yl 4-methylbenzenesulfonate (212f)

To a flame-dried flask was added KOtBu (621 mg, 1.6 equiv, 5.54 mmol) and THF (9 mL). This solution was cooled to 0 ºC and vinyl tosylate **230** (1.68 g, 1.0 equiv, 3.46 mmol) was added dropwise as a solution in THF (9 mL). This solution was stirred at 0 ºC for 2 hours. To this was added solid toluenesulfonic anhydride (1.8 g, 1.6 equiv, 5.54 mmol). This solution was allowed to warm to room temperature and stirred for 1.5 hours. The reaction was diluted with ethyl acetate (15 mL) and water (15 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica flash column chromatography (25% diethyl ether in hexanes) to give vinyl tosylate **212f** (620 mg, 28% yield). The olefin isomer is assigned to be *E* on the basis of ^{1}H NOESY NMR (observe NOE correlations between tosylate and piperidine fragments). Consistent with this assignment, the chemical shift of the allylic methylene protons (2.66 ppm in $CDCl_3$) is congruent to similarly reported *E* diaryl vinyl tosylates (typically ~2.7 ppm for allylic methylene in $CDCl_3$), which are distinct from the reported *Z* isomer chemical shift (typically ~2.3 ppm for allylic methylene of corresponding *Z* vinyl tosylate in $CDCl_3$).[35]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 2H), 7.13 – 7.08 (m, 2H), 6.95 – 6.91 (m, 2H), 6.81 – 6.77 (m, 2H), 6.73 – 6.68 (m, 2H), 6.47 – 6.41 (m, 2H), 3.89 – 3.80 (m,

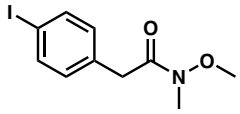
2H), 3.75 (s, 3H), 3.68 (s, 3H), 2.89 (t, J = 12.0 Hz, 2H), 2.66 (d, J = 6.5 Hz, 2H), 2.37 (s, 3H), 1.73 – 1.67 (m, 2H), 1.42 – 1.26 (m, 3H).

^{13}C NMR = (101 MHz, $CDCl_3$) δ 159.2, 158.8, 144.5, 144.4, 134.7, 131.4, 130.7, 130.5, 130.4, 129.4, 128.1, 126.2, 120.2 (q, J = 323.9 Hz), 114.0, 113.1, 55.3, 55.2, 46.8, 38.8, 33.3, 31.5, 21.7.

^{19}F NMR (282 MHz, $CDCl_3$) δ -75.2.

FT-IR (neat film NaCl): 2933, 2838, 1606, 1573, 1510, 1464, 1385, 1291, 1248, 1226, 1176, 1150, 1115, 1067, 1033, 969, 942, 837, 783, 732, 708, 668 cm^{-1}.

HR-MS (ESI) m/z: [M+Na]+ Calculated for $C_{30}H_{32}F_3NNaO_7S_2$: 662.1464; Measured: 662.1485.



2-(4-iodophenyl)-*N*-methoxy-*N*-methylacetamide (231)

Prepared according to similar published procedures,[32] to a flame-dried flask was added commercially-available 2-(4-iodophenyl)acetic acid (5.0 g, 1.0 equiv, 19.1 mmol), N,O-dimethylhydroxylammonium chloride (2.8 g, 1.5 equiv, 28.6 mmol), and EDCI (5.5 g, 1.5 equiv, 28.6 mmol). While under N_2 atmosphere, 80 mL of dry DCM was then added. Then, DMAP (3.50 g, 1.5 equiv, 28.6 mmol) was added as a solid in one portion and the mixture was allowed stir overnight under N_2 at room temperature. The next morning, the reaction was quenched with water and extracted with DCM (x3). The combined organics were washed with 1M HCl twice, then washed with brine, then dried over Na_2SO_4 and filtered.

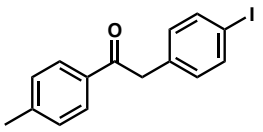
Concentration afforded a tan solid that was pure by NMR, and was taken forward as is (5.4 g, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.58 (m, 2H), 7.09 – 6.99 (m, 2H), 3.71 (s, 2H), 3.63 (s, 3H), 3.19 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 137.6, 134.6, 131.5, 92.3, 61.4, 38.9, 32.3.

FT-IR (neat film NaCl): 2932, 1670, 1400, 998, 682 cm $^{-1}$.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{10}H_{13}INO_2$: 305.9985; Measured: 305.9988.



2-(4-iodophenyl)-1-(*p*-tolyl)ethan-1-one (232) was prepared according to similar reported procedure.[33] Magnesium turnings (818 mg, 1.8 equiv, 33.63 mmol) were flame-dried under high vacuum in a round bottom flask (x3) then suspended in dry THF (144 mL). 1-Bromo-4-methylbenzene (6.66 g, 2.2 equiv, 38.9 mmol) was added followed by a small grain of I_2. The solution was allowed to stir with gentle heating *via* a heat gun until the purple-brown color of the I_2 disappears. The suspension was then stirred until all the magnesium chunks are visibly consumed. At this point, the reaction is cooled to 0 ºC then Weinreb amide **231** (5.40 g, 1.0 equiv, 17.70 mmol) was added dropwise. The reaction is monitored closely by TLC to determine starting material consumption (usually 5–20 minutes), then quenched with 30 mL saturated ammonium chloride while at 0 ºC. The reaction is extracted with diethyl ether (x3), then the combined organics are washed with brine, dried over $MgSO_4$, filtered through a short pad of silica (wash through with diethyl ether), and concentrated *in vacuo*. Pure material was obtained *via* silica flash column

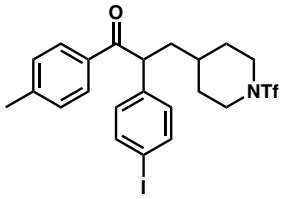
chromatography (15% ethyl acetate/hexanes with 2% DCM to help with solubility), furnishing ketone **232** as a white solid (2.85 g, 48% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.79 (m, 2H), 7.74 – 7.51 (m, 2H), 7.30 – 7.19 (m, 2H), 7.07 – 6.87 (m, 2H), 4.18 (s, 2H), 2.39 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.8, 144.4, 137.8, 134.5, 134.0, 131.7, 129.5, 128.8, 92.5, 44.9, 21.8.

FT-IR (neat film NaCl): 2933, 1677, 1606, 1482, 1444, 1385, 1252, 1183, 1146, 1049, 1006, 948, 815, 765, 709 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{10}H_{13}INO_2$: 337.0084; Measured: 337.0084.



2-(4-iodophenyl)-1-(*p*-tolyl)-3-(1-((trifluoromethyl)sulfonyl)piperidin-4-yl)propan-1-one (233)

To a flamed-dried flask was added KOtBu (0.88 g, 1.1 equiv, 7.9 mmol). This flask was evacuated under vacuum and backfilled with nitrogen three times. To this was added THF (11 mL), and the flask was cooled to 0 ºC. To this flask was added ketone **232** (2.4 g, 1.0 equiv, 7.1 mmol) in THF (15 mL), and the solution was stirred at 0 ºC for 20 minutes. To this was added a solution of iodide **219** (2.7 g, 1.05 equiv, 7.5 mmol) in THF (10 mL). The reaction flask was allowed to warm up to room temperature overnight, and quenched by addition of saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with ethyl acetate (3x 15 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by

silica flash column chromatography (15% ether in hexanes) to yield ketone **233** as a white solid (2.7 g, 67% yield).

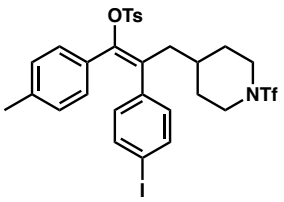
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.25 – 7.17 (m, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 4.65 – 4.54 (m, 1H), 3.90 (tq, *J* = 13.0, 2.0 Hz, 2H), 2.93 (q, *J* = 13.4 Hz, 2H), 2.37 (s, 3H), 2.18 (ddd, *J* = 14.4, 8.0, 6.6 Hz, 1H), 1.87 (dt, *J* = 12.7, 2.7 Hz, 1H), 1.79 – 1.70 (m, 2H), 1.42 – 1.25 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.4, 144.5, 139.2, 138.3, 133.8, 130.1, 129.6, 128.9, 120.2 (q, *J* = 323.5 Hz), 92.9, 49.6, 46.8, 40.1, 33.0, 32.1, 32.0, 21.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ -75.1

FT-IR (neat film NaCl): 2933, 1677, 1606, 1482, 1444, 1385, 1226, 1183, 1146, 1049, 1006, 948 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{22}H_{24}F_3INO_3S$: 566.0468; Measured: 566.0466.



(*E*)-2-(4-iodophenyl)-1-(*p*-tolyl)-3-(1-((trifluoromethyl)sulfonyl)piperidin-4-yl)prop-1-en-1-yl 4-methylbenzenesulfonate (212g)

To a flame-dried flask was added KOtBu (302 mg, 1.6 equiv, 2.69 mmol) and THF (4.4 mL). This solution was cooled to 0ºC and ketone **233** (0.950 g, 1.0 equiv, 1.68 mmol) was added dropwise as a solution in THF (4.4 mL). This solution was stirred at 0 ºC for 2 hours. To this was quickly added solid toluenesulfonic anhydride (877 mg, 1.6 equiv, 2.69 mmol).

This solution was allowed to warm to room temperature and stirred for 1.5 hours. The reaction was diluted with ethyl acetate (15 mL) and water (15 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica flash column chromatography (25% ether in hexanes) to deliver vinyl tosylate **212g** (475 mg, 39% yield). The olefin isomer is assigned to be *E* on the basis of NOESY NMR (observe NOE correlations between tosylate and piperidine fragments). Consistent with this assignment, the chemical shift of the allylic methylene protons (2.67 ppm in $CDCl_3$) is congruent to similarly reported *E* diaryl vinyl tosylates (typically ~2.7 ppm for allylic methylene in $CDCl_3$), which are distinct from the reported *Z* isomer chemical shift (typically ~2.3 ppm for allylic methylene of corresponding *Z* vinyl tosylate in $CDCl_3$).[35]

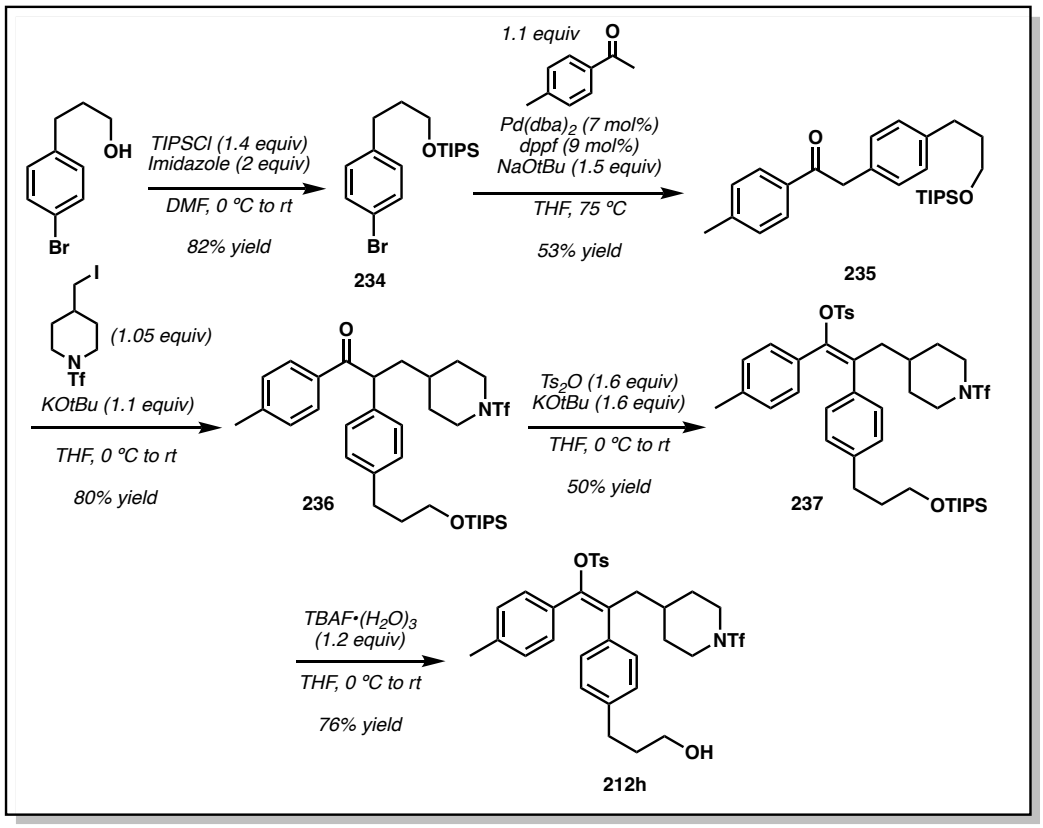
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.13 – 7.05 (m, 2H), 6.80 – 6.70 (m, 6H), 3.85 (dd, J = 13.2, 3.9 Hz, 2H), 3.05 – 2.79 (m, 2H), 2.67 (d, J = 5.9 Hz, 2H), 2.37 (s, 3H), 2.20 (s, 3H), 1.74 – 1.64 (m, 2H), 1.42 – 1.24 (m, 5H).

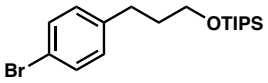
^{13}C NMR = (101 MHz, $CDCl_3$) δ 145.5, 144.7, 138.5, 138.0, 137.7, 134.4, 131.3, 130.7, 130.2, 123.0, 129.4, 128.5, 128.0, 120.2 (app q, J = 323.7 Hz), 93.2, 46.7, 38.7, 33.3, 31.7, 31.5, 22.8, 21.7, 21.4, 14.3.

^{19}F NMR (282 MHz, $CDCl_3$) δ -75.2.

FT-IR (neat film NaCl): 2921, 1597, 1483, 1446, 1387, 1226, 1177, 1150, 1115, 1049, 973, 942, 849, 825, 763, 724, 708 cm^{-1}.

HR-MS (ESI) m/z: [M+Na]+ Calculated for $C_{29}H_{29}F_3INNaO_5S_2$: 742.0376; Measured: 742.0385.





(3-(4-bromophenyl)propoxy)triisopropylsilane (234)

To a flame-dried flask equipped with a stir bar was added imidazole (3.1g, 2.0 equiv, 46.49 mmol), commercially available 3-(4-bromophenyl)propan-1-ol (5.0 g, 1.0 equiv, 23.25 mmol), and DMF (29 mL). The solution is then cooled to 0 ºC and allowed to stir for 20 minutes before adding neat TIPS–Cl dropwise. The reactions was completed after 2 hours by TLC analysis (15% diethyl ether in hexanes). The reaction was quenched with saturated ammonium chloride and extracted with 1% diethyl ether in pentane (x3), and the combined organics were washed with water, then brine, then filtered through a pad of silica gel, then concentrated *in vacuo*. Further purification of the crude material was achieved *via* silica

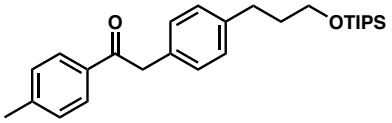
flash column chromatography (3% diethyl ether in hexanes) to afford aryl bromide **234** as a colorless oil (7.1 g, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.35 (m, 2H), 7.12 – 7.04 (m, 2H), 3.70 (t, *J* = 6.2 Hz, 2H), 2.71 – 2.63 (m, 2H), 1.88 – 1.77 (m, 2H), 1.17 – 1.00 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.4, 131.4, 130.4, 119.5, 62.4, 34.6, 31.6, 18.1, 12.1.

FT-IR (neat film NaCl): 2942, 2865, 1488, 1461, 1387, 1247, 1107, 1072, 1011, 882, 809, 717, 67 cm^{-1}.

HR-MS (FD) m/z: [M•]+ Calculated for $C_{18}H_{31}BrOSi$: 370.1328; Measured: 370.1298.



1-(*p*-tolyl)-2-(4-(3-((triisopropylsilyl)oxy)propyl)phenyl)ethan-1-one (235)

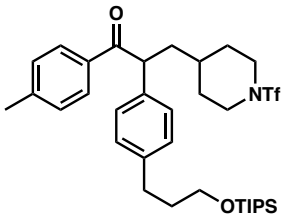
Following a reported procedure,[38] a flame-dried Schlenk flask was charged with NaO*t*Bu (2.56 g, 1.5 equiv, 26.65 mmol) and dppf (886 mg, 0.09 equiv, 1.59 mmol). The flask was evacuated and back-filled with N_2 (x3). Then, degassed THF (36 mL) was added followed by aryl bromide **234** (6.60 g, 1.0 equiv, 17.77 mmol), followed by $Pd(dba)_2$ (715 mg, 0.07 equiv, 1.24 mmol). After 5 minutes of stirring, commercially-available 1-(*p*-tolyl)ethan-1-one (2.62 g, 1.1 equiv, 19.55 mmol) was then added. The flask was then sealed with a glass stopper and heated to 75 ºC overnight. The next morning, the reaction was quenched with water and extracted with diethyl ether (x3) and the combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Silica flash chromatography (4% diethyl ether in hexanes) afforded pure ketone **235** as a slightly-yellow oil (4.0 g, 53% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.89 (m, 2H), 7.28 – 7.20 (m, 2H), 7.23 – 7.13 (m, 4H), 4.22 (s, 2H), 3.72 (t, *J* = 6.3 Hz, 2H), 2.74 – 2.65 (m, 2H), 2.39 (s, 3H), 1.91 – 1.80 (m, 2H), 1.18 – 1.01 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.4, 143.9, 140.9, 134.2, 132.0, 129.3, 129.2, 128.8, 62.6, 45.1, 34.6, 31.8, 21.7, 18.1, 12.1.

FT-IR (neat film NaCl): 3024, 2941, 2891, 2864, 2726, 1900. 1806, 1678, 1606, 1572, 1513, 1463, 1381, 1328, 1276, 1222, 1196, 1180, 1149, 1104, 1066, 1013, 996, 964, 918, 882, 809, 770, 721, 681, 658 cm^{-1}.

HR-MS (ESI) m/z: [M+K]+ Calculated for $C_{27}H_{40}KO_2Si$: 463.2429; Measured: 463.2428



1-(*p*-tolyl)-3-(1-((trifluoromethyl)sulfonyl)piperidin-4-yl)-2-(4-(3-((triisopropylsilyl)oxy)propyl)phenyl)propan-1-one (236)

To a flame-dried flask was added ketone **235** (3.95 g, 1.0 equiv, 9.3 mmol) then dissolved in THF (30 mL) and cooled to 0 ºC. In a separate flask, a freshly-prepared solution of KO*t*Bu (1.14 g, 1.1 equiv, 10.2 mmol) in THF (30 mL) was added dropwise to the ketone while at 0 ºC. The yellow solution was allowed to stir at 0 ºC for 20 minutes. Then, a solution of iodide **219** (3.48 g, 1.05 equiv, 9.7 mmol) in THF (10 mL) was added dropwise then allowed to warm to room temperature overnight. The next morning, the reaction was quenched with saturated ammonium chloride and extracted with diethyl ether (x3). The combined organics were washed once with brine, dried over Na_2SO_4, filtered, concentrated

in vacuo, and purified by silica flash column chromatography (10% diethyl ether in hexanes) to yield ketone **236** as a white solid (4.9 g, 81% yield).

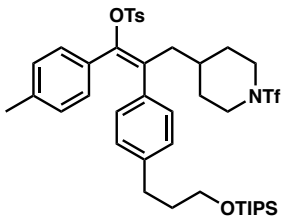
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.84 (m, 2H), 7.23 – 7.16 (m, 4H), 7.13 (d, *J* = 8.1 Hz, 2H), 4.64 (t, *J* = 7.4 Hz, 1H), 3.97 – 3.83 (m, 2H), 3.67 (t, *J* = 6.3 Hz, 2H), 3.01 – 2.86 (m, 2H), 2.69 – 2.61 (m, 2H), 2.36 (s, 3H), 2.26 – 2.14 (m, 1H), 1.95 – 1.69 (m, 5H), 1.50 – 1.24 (m, 3H), 1.15 – 0.94 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.9, 144.0, 141.4, 136.6, 134.1, 129.4, 129.3, 128.9, 127.9, 120.2 (q, *J* = 323.6 Hz), 62.6, 49.8, 46.8, 40.1, 34.5, 32.9, 32.0 (d, *J* = 9.3 Hz), 31.7, 21.6, 18.1, 12.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ -75.1 (br s).

FT-IR (neat film NaCl): 2941, 2865, 1679, 1606, 1461, 1389, 1227, 1182, 1147, 1110, 1052, 997, 949, 882, 818, 763, 709, 680 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{34}H_{51}F_3NO_4SSi$: 654.3254; Measured: 654.3266.



(*E*)-1-(*p*-tolyl)-3-(1-((trifluoromethyl)sulfonyl)piperidin-4-yl)-2-(4-(3-((triisopropylsilyl)oxy)propyl)phenyl)prop-1-en-1-yl 4-methylbenzenesulfonate (237)

To a flame-dried flask was added ketone **236** (4.70 g, 1.0 equiv, 7.20 mmol) then dissolved in THF (35 mL) and cooled to 0 ºC. In a separate flask, a freshly-prepared solution of KO*t*Bu (1.29 g, 1.60 equiv, 11.52 mmol) in THF (25 mL) was added dropwise to the ketone

while at 0 ºC. The yellow solution was allowed to stir at 0 ºC for 90 minutes. Then, Ts_2O (3.76 g, 1.6 equiv, 11.52 mmol) was added as a solid in one portion to the enolate solution with vigorous stirring then allowed to warm to room temperature (solution turns thick). After the reaction was completed by TLC analysis (20% diethyl ether in hexanes), the reaction was quenched with water and extracted with diethyl ether (x3). The combined organics were washed once with brine, dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica flash column chromatography (15% diethyl ether in hexanes) to yield pure **237** as a white solid (2.90 g, 50% yield). The olefin isomer is assigned to be *E* on the basis of NOESY NMR (observe NOE correlations between tosylate and piperidine protons, as well as between the two aryl rings). Consistent with this assignment, the chemical shift of the allylic methylene protons (2.68 ppm in $CDCl_3$) is congruent to similarly reported *E* diaryl vinyl tosylates (typically ~2.7 ppm for allylic methylene in $CDCl_3$), which are distinct from the reported *Z* isomer chemical shift (typically ~2.3 ppm for allylic methylene of corresponding *Z* vinyl tosylate in $CDCl_3$).[35]

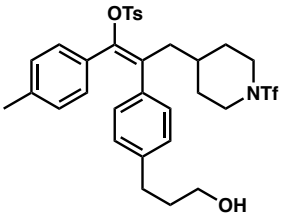
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.41 (m, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 7.01 (d, *J* = 8.2 Hz, 2H), 6.96 – 6.89 (m, 2H), 6.75 (d, *J* = 8.3 Hz, 2H), 6.70 (d, *J* = 8.1 Hz, 2H), 3.85 (dd, *J* = 13.4, 3.8 Hz, 2H), 3.65 (t, *J* = 6.3 Hz, 2H), 2.95 – 2.85 (m, 2H), 2.71 – 2.60 (m, 4H), 2.37 (s, 3H), 2.18 (s, 3H), 1.87 – 1.67 (m, 4H), 1.47 – 1.29 (m, 3H), 1.15 – 0.98 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7, 144.5, 141.5, 137.8, 135.4, 134.4, 131.6, 130.7, 129.8, 129.2, 129.1, 128.6, 128.2, 128.0, 120.2 (q, *J* = 323.8 Hz), 62.4, 46.7, 38.8, 34.2, 33.0, 31.7, 31.4, 21.5, 21.2, 17.7, 12.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ -75.3 (br s).

FT-IR (neat film NaCl): 3027, 2939, 2866, 1598, 1511, 1463, 1393, 1333, 1245, 1227, 1171, 1151, 1101, 1070, 1049, 972, 942, 910, 882, 850, 815, 781, 736, 708, 684 cm^{-1}.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{41}H_{57}F_3NO_6S_2Si$: 808.3349; Measured: 808.3371.



(*E*)-2-(4-(3-hydroxypropyl)phenyl)-1-(*p*-tolyl)-3-(1-((trifluoromethyl)sulfonyl)piperidin-4-yl)prop-1-en-1-yl 4-methylbenzenesulfonate (212h)

To a scintillation vial equipped with a stir bar was added silyl ether **237** (2.20 g, 1.0 equiv, 2.72 mmol), followed by dry THF (5 mL). The solution was cooled to 0 ºC then a freshly prepared solution of TBAF•$(H_2O)_3$ (1.03 g, 1.2 equiv, 3.26 mmol) in 5 mL of dry THF was added dropwise then allowed to warm to room temperature. After 30 minutes, reaction was completed by TLC analysis. The reaction was quenched with saturated ammonium chloride and subsequently extracted with ethyl acetate (x3). The combined organics were dried over Na_2SO_4, filtered, concentrated *in vacuo,* then purified by silica flash chromatography (20% → 50% → 70% ethyl acetate in hexanes) to afford pure alcohol **212h** as a white solid (1.35 g, 76% yield). The olefin isomer is assigned to be *E* as it was directly derived from compound **237**, which was characterized to be the *E* vinyl tosylate. To further validate this, NOESY NMR was conducted and validated this assignment (observe NOE correlations between tosylate and piperidine protons, as well as between the two aryl rings).[35]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (app d, *J* = 8.4 Hz, 2H), 7.09 (app d, *J* = 8.5 Hz, 2H), 7.00 (app d, *J* = 8.2 Hz, 2H), 6.92 (app d, *J* = 8.2 Hz, 2H), 6.77 – 6.66 (m, 4H), 3.85 (dd, *J* = 13.1, 4.0 Hz, 2H), 3.63 (t, *J* = 6.4 Hz, 2H), 2.90 (t, *J* = 12.0 Hz, 2H), 2.70 – 2.59 (m, 4H), 2.37 (s, 3H), 2.18 (s, 3H), 1.90 – 1.79 (m, 2H), 1.75 – 1.67 (m, 2H), 1.45 – 1.27 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9, 144.6, 141.1, 138.0, 135.8, 134.5, 131.6, 130.7, 129.9, 129.4, 129.3, 128.6, 128.3, 128.0, 62.3, 46.7, 38.8, 34.0, 33.2, 31.8, 31.5, 21.7, 21.3.

*CF_3 quartet not apparent.

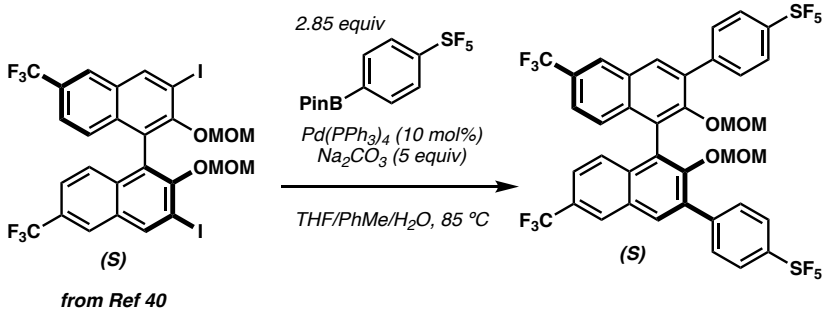
^{19}F NMR (376 MHz, $CDCl_3$) δ -75.3 (br s).

FT-IR (neat film NaCl): 3300, 2931, 1386, 1226, 1176, 1151, 1050, 968, 942, 825 cm^{-1}.

HR-MS (ESI) m/z: $[M+NH_4]+$ Calculated for $C_{32}H_{40}F_3N_2O_6S_2$: 669.2280; Measured: 669.2287.

4.5.3 Preparation of Catalysts

***Synthesis of binol precursors**:*



from Ref 40

(*S*)-((2,2'-bis(methoxymethoxy)-6,6'-bis(trifluoromethyl)-[1,1'-binaphthalene]-3,3'-diyl)bis(4,1-phenylene))bis(pentafluoro- λ6**-sulfane) (238)**

Following a similar reported procedure,[39] MOM-protected (*S*)-3,3'-diiodo-6,6'-bis(trifluoromethyl)-BINOL (prepared according to published protocol[40]) (5.0 g, 1.0 equiv, 6.56 mmol) was added to an oven-dried Schlenk flask, followed by Na_2CO_3 (3.5 g, 5 equiv, 32.80 mmol), and *p*-SF_5 aryl BPin (6.50 g, 3.0 equiv, 19.7 mmol). The flask was vac/backfilled with N_2 three times, then THF (112 mL), toluene (112 mL), and water (60 mL) were added. The mixture was the degassed by sparging with nitrogen while vigorously stirring for 30 minutes. Then, under positive N_2 gas flow, solid $Pd(PPh_3)_4$ (758 mg, 0.1 equiv, 0.65 mmol) was added in one portion. The flask was then sealed and heated to 85 ºC overnight. The next morning, starting material had been consumed by TLC. Water was added to the reaction and extracted with ethyl acetate three times. The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified *via* flash chromatography (4% diethyl ether in hexanes) to obtain MOM BINOL **238** mixed with the starting aryl Bpin, but was carried forward to the deprotection step as is (*see next step*).

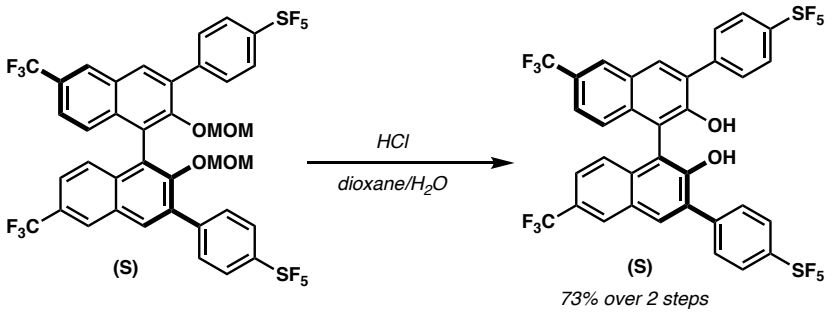
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 2H), 8.10 (s, 2H), 7.94 – 7.82 (m, 8H), 7.52 (dd, *J* = 9.0, 1.9 Hz, 2H), 7.38 (d, *J* = 8.9 Hz, 2H), 4.40 (s, 4H), 2.36 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2 – 152.1 (m), 141.7, 135.1, 135.0, 132.2, 129.9, 129.6, 128.1, 127.8, 127.4, 126.4, 126.3 (m), 126.0, 122.1, 99.3, 56.2. ******CF_3 carbon (typically a quartet) difficult to see due to peak overlap, not included.*

^{19}F NMR (376 MHz, $CDCl_3$) δ 85.60 – 82.21 (m), 63.02 (d, *J* = 149.7 Hz), -62.44.

FT-IR (neat film NaCl): 2981, 1634, 1602, 1448, 1436, 1398, 1362, 1331, 1293, 1249, 1194, 1164, 1144, 1129, 1100, 1082, 1068, 1002, 963, 916, 836, 738, 654 cm^{-1}.

HR-MS (FD) m/z: [M•]+ Calculated for $C_{38}H_{26}F_{16}O_4S_2$: 914.1017; Measured: 914.1002.



(*S*)-3,3'-bis(4-(pentafluoro-λ 6-sulfaneyl)phenyl)-6,6'-bis(trifluoromethyl)-[1,1'-binaphthalene]-2,2'-diol (239)

MOM-protected BINOL **238** was dissolved in 1,4-dioxane (42 mL). Then, 9 mL of 6 M aq. HCl was added dropwise. The reaction was then sealed and heated to 85 ºC overnight, by which time starting material is consumed by TLC forming a more polar spot. Saturated aqueous bicarbonate solution was then added (~35 mL), and the mixture was extracted with DCM three times. The combined organics were washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified *via* flash chromatography (10% ethyl acetate in hexanes) to obtain BINOL **239** as a white solid (4.0 g, 73% yield over two steps from diiodo precursor).

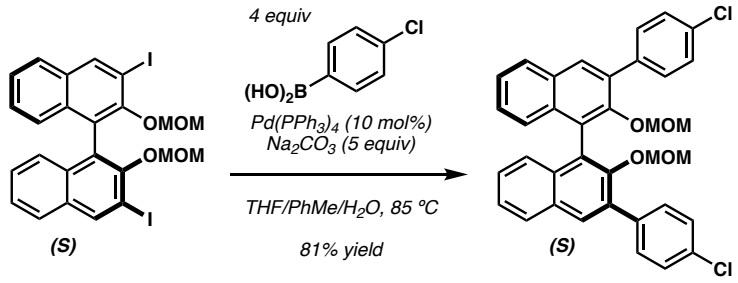
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 – 8.26 (m, 2H), 8.18 (s, 2H), 7.99 – 7.87 (m, 4H), 7.83 (d, *J* = 8.6 Hz, 4H), 7.56 (dd, *J* = 8.9, 1.9 Hz, 2H), 7.33 – 7.24 (m, 2H), 5.44 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1–152.9 (m), 151.9, 140.0, 134.6, 133.3, 130.3, 130.0, 128.4, 127.4, 127.1, 126.7 (m), 126.3 (m), 125.1, 124.2 (q, *J* = 272.1 Hz), 111.9.

^{19}F NMR (376 MHz, $CDCl_3$) δ 84.1 (p, *J* = 150.3 Hz), 62.9 (d, *J* = 149.8 Hz), -62.3.

FT-IR (neat film NaCl): 3534, 2341, 1632, 1608, 1502, 1452, 1400, 1334, 1317,1294, 1241, 1198, 1175, 1163, 1131, 1101, 1071, 945, 911, 836, 780, 739, 708, 667, 624, 604 cm^{-1}.

HR-MS (ESI) m/z: [M-H]- Calculated for $C_{34}H_{17}F_{16}O_2S_2$: 825.0420; Measured: 825.0415.



(*S*)-3,3'-bis(4-chlorophenyl)-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (240)

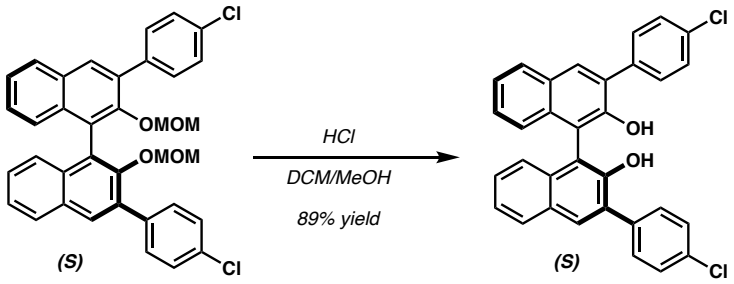
Following a similar procedure as above[39], MOM-protected 3,3'-diiodo BINOL (1.40 g, 1 equiv, 2.24 mmol) was added to an oven-dried Schlenk flask, followed by Na_2CO_3 (1.18 g, 5 equiv, 11.2 mmol), and the aryl boronic acid (1.4 g, 4 equiv, 8.94 mmol). The flask was vac/backfilled with N_2 three times, then THF (38 mL), toluene (38 mL), and water (18 mL) were added. The mixture was the degassed by sparging with nitrogen while vigorously stirring for 30 minutes. Then, under positive N_2 gas flow, solid $Pd(PPh_3)_4$ (258 mg, 0.1 equiv, 0.224 mmol) was added in one portion. The flask was then sealed and heated to 85 ºC overnight. The next morning, starting material had been consumed by TLC. Water was added to the reaction and extracted with ethyl acetate three times. The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified *via* flash chromatography (2.5% diethyl ether in hexanes) to obtain MOM BINOL **240** as a white solid (1.1 g, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 2H), 7.90 (d, J = 8.2 Hz, 2H), 7.75 – 7.68 (m, 4H), 7.49 – 7.41 (m, 6H), 7.33 – 7.26 (m, 4H), 4.40 (dd, J = 5.9, 0.6 Hz, 2H), 4.35 (dd, J = 5.9, 0.6 Hz, 2H), 2.37 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.3, 137.6, 134.4, 133.8, 133.6, 131.1, 130.9, 130.7, 128.7, 128.0, 126.7, 126.7, 126.5, 125.5, 98.8, 56.1.

FT-IR (neat film NaCl): 2930, 1590, 1492, 1427, 1387, 1352, 1246, 1157, 1091, 1015, 996, 967, 909, 830, 750, 731 cm $^{-1}$.

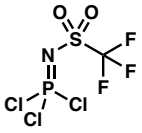
HR-MS (ESI) m/z: [M+Na]+ Calculated for $C_{36}H_{28}Cl_2NaO_4$: 617.1257; Measured: 617.1255.



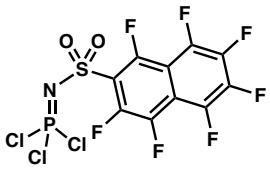
(*S*)-3,3'-bis(4-chlorophenyl)-[1,1'-binaphthalene]-2,2'-diol (241)

MOM-protected BINOL **240** was dissolved in 54 mL of DCM/MeOH (1:1) in an oven-dried flask equipped with a stir bar. Then, 2.7 mL of conc. HCl is added slowly dropwise. The mixture is allowed to stir at room temperature overnight, by which time starting material is consumed by TLC forming a more polar spot. Saturated aqueous bicarbonate solution was then added (~40 mL), and the mixture was extracted with DCM three times. The combined organics were washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified *via* flash chromatography (10% diethyl ether in hexanes) to obtain BINOL **241** a white solid (818 mg, 89% yield), which matched published NMR spectra.[41]

***Preparation of phosphorimidoyl trichloride**:* prepared according to procedures published by List from the corresponding sulfonamide:

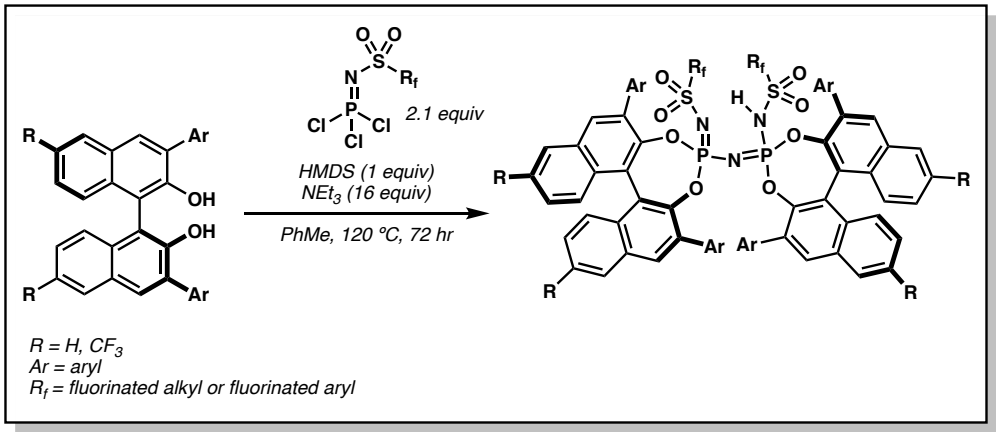


((trifluoromethyl)sulfonyl)phosphorimidoyl trichloride (242) was prepared according to published procedures.[42]



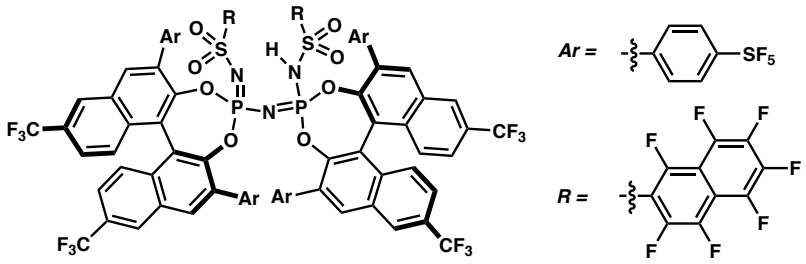
((perfluoronaphthalen-2-yl)sulfonyl)phosphorimidoyl trichloride (243) was prepared according to published procedures.[19]

Preparation of IDPi catalysts:



All IDPi catalysts were made in a similar manner as reported by List *et al*.[43] An oven-dried Schlenk flask was cycled into an inert atmosphere glovebox, and the corresponding

phosphorimidoyl trichloride was weighed into it (2.1 equiv). The Schlenk flask was then sealed with a septa, brought out of the glovebox, and put under N_2 atmosphere. To the Schlenk flask was then added dry toluene solvent (to achieve 0.33 M in BINOL), followed by the BINOL under positive N_2 flow (2.1 equiv). In cases where the phosphorimidoyl trichloride reagent is a solid, the BINOL was added first followed by toluene. To the homogeneous solution was added freshly distilled (over CaH_2) triethylamine (16 equiv) and the mixture was allowed to stir at room temperature. After 20 minutes of stirring at room temperature, dried HMDS (distilled over CaH_2) was added dropwise (1 equiv), then the Schlenk flask was sealed with a ground glass stopper and heated at 120 ºC while sealed for 3 days. After this time, the reaction was cooled to room temperature, quenched with 1M HCl, and allowed to stir vigorously for 10 minutes before extracting the mixture with DCM (x3). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by silica flash chromatography (0% → 10% ethyl acetate in benzene) to obtain pure IDPi after concentration *in vacuo*. This material was then dissolved in DCM and stirred vigorously with 6M aq. HCl for 10 minutes. The DCM layer is separated out and washed once more with 6M aq. HCl. The DCM layer was concentrated down, and azeotroped from dry toluene (x3), then dry benzene (x2), then dry DCM/Hex to obtain typically white or off-white solids which are further dried under high vacuum over P_2O_5 overnight before cycling into an inert atmosphere glovebox.



IDPi-211

^{1}H NMR (400 MHz, d_6-DMSO) δ 8.85 (s, 2H), 8.76 (s, 2H), 8.68 (s, 2H), 8.53 (s, 2H), 8.09 – 7.97 (m, 8H), 7.82 (dd, *J* = 9.2, 1.9 Hz, 2H), 7.41 – 7.32 (m, 2H), 7.21 (d, *J* = 8.6 Hz, 4H), 7.00 (t, *J* = 9.3 Hz, 4H), 6.59 (d, *J* = 8.6 Hz, 4H).

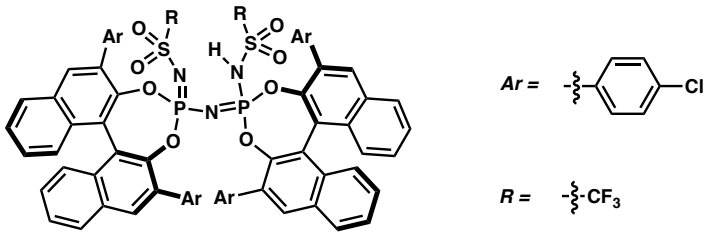
^{13}C NMR (101 MHz, d_6-DMSO) δ 152.4 – 152.0 (m), 151.5 – 151.2 (m), 149.9 – 149.1 (m), 146.7 – 146.4 (m), 145.5 (t, *J* = 6.4 Hz), 145.0 (t, *J* = 4.9 Hz), 144.2 – 143.7 (m), 142.6 – 142.2 (m), 141.6 – 141.3 (m), 140.8 – 139.8 (m), 139.4 – 139.0 (m), 138.7, 138.5, 138.2 – 137.6, 136.9 – 136.5 (m), 133.1, 132.8, 132.4, 132.3, 131.9, 131.5, 130.5, 129.8, 129.5, 128.8, 128.3, 128.1, 128.0, 127.3, 126.9, 126.7, 126.5, 126.2, 125.9, 125.5, 125.3, 125.2, 124.0, 122.8 (m), 122.6, 122.2, 121.7, 120.1, 119.9, 110.0 – 109.6 (m), 106.9 – 106.3 (m). *other peaks not apparent.

^{19}F NMR (376 MHz, d_6-DMSO) δ 87.0 (m), 64.3 (d, *J* = 255.0 Hz), 63.9 (d, *J* = 254.6 Hz), -61.0, -61.2 – -61.8 (m), -113.8 (dd, *J* = 77.4, 18.0 Hz), -133.9 (d, *J* = 20.1 Hz), -143.3 (dt, *J* = 76.3, 17.5 Hz), -146.6 (dd, *J* = 45.9, 28.5 Hz), -149.2 (dt, *J* = 56.5, 19.4 Hz), -152.0, -155.2 (q, *J* = 14.0 Hz).

^{31}P NMR (161 MHz, d_6-DMSO) δ -1.39.

FT-IR (neat film NaCl): 1643, 1491, 1416, 1295, 1139, 1068, 960, 913, 851, 836 cm $^{-1}$.

HR-MS (ESI) m/z: [M-H]- Calculated for $C_{88}H_{32}F_{46}N_3O_8P_2S_6$: 2385.9259; Measured 2385.9247.



IDPi-209

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.97 (s, 2H), 7.93 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.71 (ddd, *J* = 8.2, 6.6, 1.4 Hz, 2H), 7.59 (dd, *J* = 8.6, 1.3 Hz, 2H), 7.56 – 7.51 (m, 2H), 7.46 (ddd, *J* = 8.2, 6.3, 1.6 Hz, 2H), 7.35 – 7.25 (m, 11H), 7.17 (d, *J* = 4.7 Hz, 3H), 6.90 – 6.80 (m, 4H), 6.39 – 6.29 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7 (t, *J* = 5.1 Hz), 143.4 (app t), 134.7, 134.1, 133.9, 133.8, 132.8, 132.6, 132.3, 132.0, 131.9, 131.8, 131.7, 131.3, 131.0, 130.4, 128.9, 128.8, 128.4, 127.8, 127.7, 127.2, 127.1, 127.0, 126.6, 123.7, 123.7, 123.6, 122.1, 119.5 (q, *J* = 321.4 Hz).

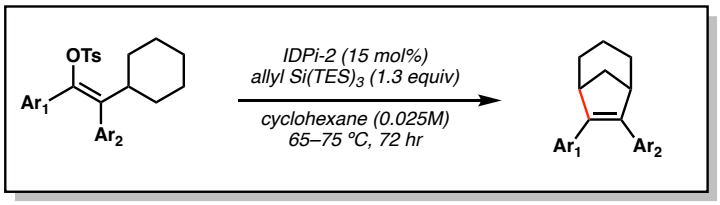
^{19}F NMR (376 MHz, $CDCl_3$) δ -78.4.

^{31}P NMR (162 MHz, $CDCl_3$) δ -13.5.

FT-IR (neat film NaCl): 2933, 1493, 1311, 1189, 1150, 1105, 990, 967, 900, 844, 829, 731 cm^{-1}.

HR-MS (ESI) m/z: [M-H]- Calculated for $C_{66}H_{36}Cl_4F_6N_3O_8P_2S_2$: 1380.0053; Measured 1380.0050.

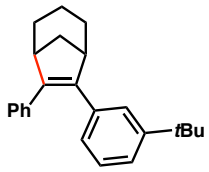
4.5.4 Catalytic Asymmetric C–H Insertion Reactions of Vinyl Cations



General Procedure A: ***C–H insertion into appended cyclohexyl ring***

All C–H insertion reactions were conducted in a well-maintained glove box (O_2, H_2O <0.5 ppm) on 0.15 mmol scale unless otherwise noted. To a dram vial equipped with a magnetic stir bar was added **IDPi-209** catalyst (15 mol%) followed by cyclohexane solvent (dried over potassium) to achieve 0.025M relative to vinyl tosylate. Then, 2-allyl-1,1,1,3,3,3-hexaethyl-2-(triethylsilyl)trisilane (1.3 equiv) was added. To this mixture was then added the corresponding vinyl tosylate in solid form in one portion. The reaction was then sealed with a Teflon cap and heated to 65–75 ºC for 72 hours (unless otherwise noted). (*Note*: reaction mixture is typically heterogeneous at room temperature, but readily goes homogeneous once heated with stirring and typically remains homogeneous during the entire course of the reaction until it is completed.) The reactions were monitored by TLC, typically using 5–10% diethyl ether in hexanes for the mobile phase (C–H insertion products are typically higher in R_f than the starting vinyl tosylate). Once the reaction was completed, the vial was removed from the glovebox. A few drops of triethylamine were then added then diluted with DCM. The homogeneous solution was then plugged through silica gel (pushing through with DCM), concentrated *in vacuo*, and analyzed by ^{1}H NMR using nitromethane as an internal standard for qNMR analysis. The crude material was purified by flash column chromatography (typically 0–1% benzene in hexanes or 0-1% diethyl ether in hexanes) then dried on high vacuum to obtain material that is pure by ^{1}H

NMR. The enantiomeric excess of the material was then assessed by chiral HPLC. In cases where trace impurities (<5%) were observed on the chiral HPLC trace, further purification *via* reverse phase preparatory HPLC was performed to obtain analytical quantities of high-purity material to ensure accurate enantiomeric excess determination based on peak integration.



6-(3-(*tert*-butyl)phenyl)-7-phenylbicyclo[3.2.1]oct-6-ene (205a)

Following General Procedure A: To a dram vial equipped with a stir bar was added **IDPi-209** (31.1 mg, 0.15 equiv, 0.0225 mmol), cyclohexane (6.0 mL), and 2-allyl-1,1,1,3,3,3-hexaethyl-2-(triethylsilyl)trisilane (80.9 mg, 1.3 equiv, 0.195 mmol). To this solution was added vinyl tosylate **202a** (73.3 mg, 1.0 equiv, 0.15 mmol). The reaction was sealed with a Teflon cap and heated to 65 ºC for 72 hours, then the reaction was removed from the glovebox and a few drops of triethylamine were added to quench the reaction and diluted further with DCM. This homogeneous mixture was then plugged through silica gel with DCM, concentrated *in vacuo*, and purified by flash column chromatography (1% benzene in hexanes) to give **205a** as a colorless oil (23.0 mg, 48% yield). This material was determined by chiral HPLC to be 77% ee.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.26 (m, 3H), 7.23 (ddd, J = 7.9, 6.8, 0.9 Hz, 2H), 7.18 (dd, J = 3.6, 1.6 Hz, 2H), 7.13 – 7.08 (m, 1H), 3.05 – 2.93 (m, 2H), 2.36 (dtd, J = 10.6, 4.5, 2.9 Hz, 1H), 1.82 (dddd, J = 17.8, 8.9, 5.9, 2.5 Hz, 1H), 1.72 (ddt, J = 9.3, 6.4, 2.9 Hz,

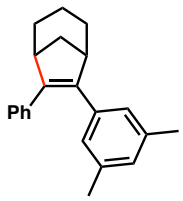
1H), 1.67 – 1.56 (m, 5H), 1.15 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.6, 139.2, 139.0, 138.4, 137.1, 128.3, 128.2, 128.0, 126.6, 125.7, 124.7, 123.5, 46.7, 46.0, 44.5, 34.6, 31.3, 26.0, 25.5, 19.5.

FT-IR (neat film NaCl): 2931, 2854, 1596, 1461, 901, 767, 698 cm $^{-1}$.

HR-MS (EI) m/z: [M$^{\bullet}$]+ Calculated for $C_{24}H_{28}$: 316.2191; Measured: 316.2182.

HPLC (CHIRALCEL ODH column) 99.9:0.1 (hex/*i*PrOH) 0.5mL/min; t_{minor} (8.02 min), t_{major} (8.43 min); 77% ee.



6-(3,5-dimethylphenyl)-7-phenylbicyclo[3.2.1]oct-6-ene (205b)

Following General Procedure A: To a dram vial equipped with a stir bar was added **IDPi-209** (31.1 mg, 0.15 equiv, 0.0225 mmol), cyclohexane (6.0 mL), and 2-allyl-1,1,1,3,3,3-hexaethyl-2-(triethylsilyl)trisilane (80.9 mg, 1.3 equiv, 0.195 mmol). To this solution was added vinyl tosylate **202b** (69.1 mg, 1.0 equiv, 0.15 mmol). The reaction was sealed with a Teflon cap and heated to 65 ºC for 72 hours, then the reaction was removed from the glovebox and a few drops of triethylamine were added to quench the reaction and diluted further with DCM. This homogeneous mixture was then plugged through silica gel with DCM, concentrated *in vacuo*, and purified by flash column chromatography (0.5% diethyl ether in hexanes) to give insertion product **205b** as a pale yellow oil (20.0 mg, 46% yield). This material was determined by chiral HPLC to be 73% ee.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.26 (m, 2H), 7.23 – 7.19 (m, 2H), 7.18 – 7.12 (m,

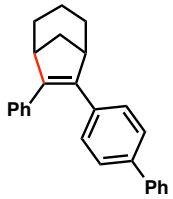
1H), 6.90 – 6.86 (m, 2H), 6.85 – 6.81 (m, 1H), 2.96 (dp, J = 13.5, 2.5 Hz, 2H), 2.35 – 2.31 (m, 1H), 2.21 (s, 6H), 1.83 (dt, J = 11.5, 4.3 Hz, 1H), 1.70 – 1.56 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.3, 138.4, 137.9, 137.7, 128.4, 128.2, 128.1, 126.5, 125.9, 46.7, 46.2, 44.5, 25.8, 25.7, 21.5, 19.5.

FT-IR (neat film NaCl): 2926, 2853, 1598, 1443, 836, 765, 694 cm $^{-1}$.

HR-MS (EI) m/z: [M$^{\bullet}$]+ Calculated for $C_{22}H_{24}$: 288.1878; Measured: 288.1874.

HPLC (CHIRALCEL ODH column) 99.9:0.1 (hex/*i*PrOH) 0.5mL/min; t_{minor} (8.37 min), t_{major} (10.82 min); 73% ee.



6-([1,1'-biphenyl]-4-yl)-7-phenylbicyclo[3.2.1]oct-6-ene (205c)

Following General Procedure A: to a dram vial equipped with a stir bar was added **IDPi-209** (31.1 mg, 0.15 equiv, 0.0225 mmol), cyclohexane (6.0 mL), and 2-allyl-1,1,1,3,3,3-hexaethyl-2-(triethylsilyl)trisilane (80.9 mg, 1.3 equiv, 0.195 mmol). To this solution was added vinyl tosylate **202c** (76.3 mg, 1.0 equiv, 0.15 mmol). The reaction was sealed with a Teflon cap and heated to 65 ºC for 72 hours, then the reaction was removed from the glovebox and a few drops of triethylamine were added to quench the reaction and diluted further with DCM. This homogeneous mixture was then plugged through silica gel with DCM, concentrated *in vacuo*, and purified by flash column chromatography (1% benzene in hexanes) to give insertion product **205c** as a white viscous oil (27.5 mg, 55% yield). This material was determined by chiral HPLC to be 73% ee.

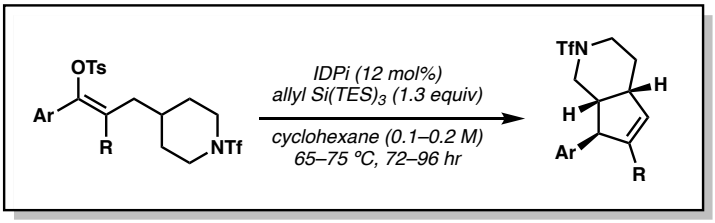
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.57 (m, 2H), 7.48 – 7.40 (m, 4H), 7.37 – 7.30 (m, 5H), 7.27 (d, *J* = 4.5 Hz, 1H), 7.26 – 7.23 (m, 2H), 7.22 – 7.17 (m, 1H), 3.10 – 2.93 (m, 2H), 2.38 (dtd, *J* = 10.6, 4.4, 2.6 Hz, 1H), 1.88 – 1.78 (m, 1H), 1.71 – 1.58 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0, 139.5, 139.2, 138.4, 138.0, 136.8, 128.9, 128.5, 128.4, 128.2, 127.3, 127.0, 126.9, 126.8, 46.7, 46.2, 44.4, 25.9, 25.7, 19.5.

FT-IR (neat film NaCl): 2924, 2853, 761, 697 cm $^{-1}$.

HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{26}H_{25}$: 337.1951; Measured: 337.1946.

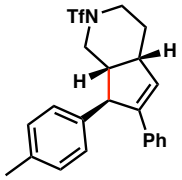
HPLC (CHIRALCEL ODH column) 99.9:0.1 (hex/*i*PrOH) 0.5mL/min; t_{minor} (11.2 min), t_{major} (13.16 min); 73%



General Procedure B: ***C–H Insertion into appended N-Tf piperidine group.***

All C–H insertion reactions were conducted in a well-maintained glove box (O_2, H_2O <0.5 ppm) on 0.1 mmol scale unless otherwise noted. To a dram vial equipped with a magnetic stir bar was added IDPi **211** catalyst followed by cyclohexane solvent (dried over potassium), followed by 2-allyl-1,1,1,3,3,3-hexaethyl-2-(triethylsilyl)trisilane. To this mixture was then added the corresponding vinyl tosylate in solid form in one portion. The reaction was then sealed with a Teflon cap and heated to 65 ºC for 72 hours (unless otherwise noted). (*Note*: reaction mixture is typically heterogeneous at room temperature, but readily goes homogeneous once heated with stirring and typically remains homogeneous during the entire course of the reaction.) The reactions were monitored by

TLC, typically using 5–15% ethyl acetate in hexanes for the mobile phase (C–H insertion products are typically higher in R_f than the starting vinyl tosylate). Once the reaction was completed, the vial was removed from the glovebox. A few drops of triethylamine were then added then diluted with DCM. The homogeneous solution was then plugged through silica gel (pushing through with 1:1 DCM/diethyl ether), concentrated *in vacuo*, and analyzed by ^{1}H NMR using nitromethane as an internal standard for qNMR analysis. The crude material was purified by flash column chromatography (typically 0–10% diethyl ether or ethyl acetate in hexanes) then dried on high vacuum to obtain material that is pure by ^{1}H NMR. The enantiomeric excess of the material was then assessed by chiral HPLC. In cases where trace impurities (<5%) were observed on the chiral HPLC trace, further purification *via* reverse phase preparatory HPLC was performed to obtain analytical quantities of high-purity material to ensure accurate enantiomeric excess determination based on peak integration. Many of the products from this reaction could be recrystallized from hexanes to obtain highly enantioenriched material (typically >99% ee) by heating in hexanes solvent and allowing to cool to room temperature or to –30 ºC. *Note*: unless otherwise noted, characterization of all C–H insertion products by NMR required heating to 90 ºC in d_6-DMSO which was necessary to prevent peak broadening of the N-Tf piperidine protons (due to the Perlin effect) and also to obtain accurate integration values.[44] Room temperature NMR in $CDCl_3$ could be used to obtain NMR yields, given that the diagnostic styrenyl olefin peak is sharp (only the N-Tf piperidine protons are broadened due to the Perlin effect).



(4a*R*,7*R*,7a*R*)-6-phenyl-7-(*p*-tolyl)-2-((trifluoromethyl)sulfonyl)-2,3,4,4a,7,7a-hexahydro-1*H*-cyclopenta[*c*]pyridine (213a)

Following General Procedure B: To a dram vial equipped with a stir bar was added **IDPi 211** (28.7 mg, 0.12 equiv, 0.012 mmol), cyclohexane (0.5 mL), and 2-allyl-1,1,1,3,3,3-hexaethyl-2-(triethylsilyl)trisilane (53.9 mg, 1.3 equiv, 0.13 mmol). To this solution was added vinyl tosylate **(*E*)-212a** (59.4 mg, 1.0 equiv, 0.1 mmol). The reaction was sealed with a teflon cap and heated to 65 ºC for 72 hours, the reaction was removed from the glovebox and a few drops of triethylamine were added to quench the reaction and diluted further with DCM. This homogeneous mixture was then plugged through silica gel with DCM/diethyl ether (1:1), concentrated *in vacuo*, and purified by flash column chromatography (4% diethyl ether in hexanes) to give insertion product **213a** as a white solid (34.1 mg, 81% yield). This solid was determined by chiral HPLC to be in 91% *ee*. *Note*: the *Z* vinyl tosylate isomer could also be used and gives rise to similar results, i.e. yield, enantioselectivity, diastereoselectivity.

^{1}H NMR (400 MHz, d_6-DMSO, 90 ºC) δ 7.39 – 7.31 (m, 2H), 7.28 – 7.21 (m, 2H), 7.21 – 7.15 (m, 1H), 7.14 – 7.07 (m, 4H), 6.40 (dd, *J* = 2.4, 1.5 Hz, 1H), 4.08 (d, *J* = 5.2 Hz, 1H), 3.73 (dd, *J* = 13.3, 5.4 Hz, 1H), 3.57 (ddd, *J* = 12.0, 7.6, 4.1 Hz, 1H), 3.47 (td, *J* = 13.1, 5.6 Hz, 2H), 3.29 – 3.11 (m, 1H), 2.39 (tt, *J* = 7.1, 5.3 Hz, 1H), 2.27 (s, 3H), 2.07 (dddd, *J* = 13.9, 7.6, 6.1, 4.1 Hz, 1H), 1.76 (dtd, *J* = 14.5, 7.5, 4.1 Hz, 1H).

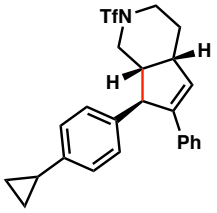
^{13}C NMR (101 MHz, d_6-DMSO, 90 ºC) δ 143.8, 138.6, 135.0, 134.9, 130.4, 128.6, 127.6, 126.9, 126.5, 125.7, 119.5 (q, J = 324.8 Hz), 52.9, 46.8, 45.6, 43.9, 26.4, 19.9.

^{19}F NMR (376 MHz, d_6-DMSO, 90 ºC) δ -75.3.

FT-IR (neat film NaCl): 2916, 1383, 1225, 1214, 1189, 1055, 1008, 764 cm^{-1}.

HR-MS (FD-MS) m/z: [M]+ Calculated for $C_{22}H_{22}F_3NO_2S$: 421.1323; Measured: 421.1317

HPLC (ChiralPak ADH column) 98:02 (hex/*i*PrOH) 1mL/min; t_{major} (4.89 min), t_{minor} (6.09 min); 91% ee.



((4a*R*,7*R*,7a*R*)-7-(4-cyclopropylphenyl)-6-phenyl-2-((trifluoromethyl)sulfonyl)-2,3,4,4a,7,7a-hexahydro-1*H*-cyclopenta[*c*]pyridine (213b)

Following General Procedure B: To a dram vial equipped with a stir bar was added **IDPi-211** (28.7 mg, 0.12 equiv, 0.012 mmol), cyclohexane (0.5 mL), and 2-allyl-1,1,1,3,3,3-hexaethyl-2-(triethylsilyl)trisilane (53.9 mg, 1.3 equiv, 0.13 mmol). To this solution was added vinyl tosylate **212b** (62.0 mg, 1.0 equiv, 0.1 mmol). The reaction was sealed with a Teflon cap and heated to 65 ºC for 72 hours, then the reaction was removed from the glovebox and a few drops of triethylamine were added to quench the reaction and diluted further with DCM. This homogeneous mixture was then plugged through silica gel with DCM/diethyl ether (1:1), concentrated *in vacuo*, and purified by flash column

chromatography (5% diethyl ether in hexanes) to give insertion product **213b** as a white solid (36.2 mg, 81% yield). This material was determined by chiral HPLC to be 92% ee.

^{1}H NMR (400 MHz, d_6-DMSO, 90 ºC) δ 7.32 – 7.28 (m, 2H), 7.23 – 7.18 (m, 2H), 7.16 – 7.12 (m, 1H), 7.09 – 7.05 (m, 2H), 6.99 – 6.95 (m, 2H), 6.36 (dd, *J* = 2.4, 1.5 Hz, 1H), 4.03 (dt, *J* = 5.1, 1.7 Hz, 1H), 3.69 (dd, *J* = 13.3, 5.4 Hz, 1H), 3.57 – 3.34 (m, 3H), 3.18 – 3.13 (m, 1H), 2.34 (tt, *J* = 7.1, 5.2 Hz, 1H), 2.02 (dddd, *J* = 13.8, 7.6, 6.1, 4.2 Hz, 1H), 1.84 (tt, *J* = 8.4, 5.1 Hz, 1H), 1.72 (dtd, *J* = 14.4, 7.4, 4.1 Hz, 1H), 0.90 – 0.85 (m, 2H), 0.62 – 0.56 (m, 2H).

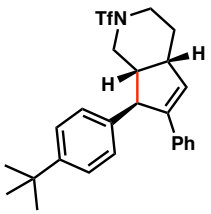
^{13}C NMR (101 MHz, d_6-DMSO, 90 ºC) δ 143.8, 141.2, 138.7, 135.0, 130.5, 127.6, 126.9, 126.6, 125.7, 125.4, 119.5 (q, *J* = 324.9 Hz), 52.9, 46.8, 45.6, 43.9, 26.4, 14.2, 8.1 (other signal not detected, likely under solvent peak).

^{19}F NMR (376 MHz, d_6-DMSO, 90 ºC) δ -75.0.

FT-IR (neat film NaCl): 2917, 1459, 1387, 1226, 1189, 1148, 952, 762 cm $^{-1}$.

HR-MS (ESI) m/z: $[M+NH_4]+$ Calculated for $C_{24}H_{28}F_3N_2O_2S$: 465.1818; Measured: 465.1816.

HPLC (ChiralPak ADH column) 98:02 (hex/*i*PrOH) 1mL/min; t_{major} (5.78 min), t_{minor} (7.01 min); 92% ee.



(4a*R*,7*R*,7a*R*)-7-(4-(*tert*-butyl)phenyl)-6-phenyl-2-((trifluoromethyl)sulfonyl)-2,3,4,4a,7,7a-hexahydro-1*H*-cyclopenta[*c*]pyridine (213c)

Following General Procedure B: To a dram vial equipped with a stir bar was added **IDPi-211** (28.7 mg, 0.12 equiv, 0.012 mmol), cyclohexane (0.5 mL), and 2-allyl-1,1,1,3,3,3-hexaethyl-2-(triethylsilyl)trisilane (53.9 mg, 1.3 equiv, 0.13 mmol). To this solution was added vinyl tosylate **212c** (63.7 mg, 1.0 equiv, 0.1 mmol). The reaction was sealed with a Teflon cap and heated to 65 ºC for 72 hours, then the reaction was removed from the glovebox and a few drops of triethylamine were added to quench the reaction and diluted further with DCM. This homogeneous mixture was then plugged through silica gel with DCM/diethyl ether (1:1), concentrated *in vacuo*, and purified by flash column chromatography (4% diethyl ether in hexanes) to give insertion product **213c** as a white solid (44.5 mg, 96% yield). This material was determined by chiral HPLC to be 88% ee.

^{1}H NMR (400 MHz, d_6-DMSO, 90 ºC) δ 7.34 – 7.30 (m, 2H), 7.30 – 7.26 (m, 2H), 7.21 (tt, *J* = 6.6, 1.0 Hz, 2H), 7.17 – 7.11 (m, 3H), 6.37 (dd, *J* = 2.4, 1.4 Hz, 1H), 4.05 (dt, *J* = 4.9, 1.7 Hz, 1H), 3.71 (dd, *J* = 13.2, 5.5 Hz, 1H), 3.48 (td, *J* = 8.0, 4.3 Hz, 2H), 3.39 (dd, *J* = 13.3, 7.3 Hz, 1H), 3.20 – 3.13 (m, 1H), 2.36 (tt, *J* = 7.3, 5.2 Hz, 1H), 2.06 – 1.98 (m, 1H), 1.74 (dtd, *J* = 14.2, 7.1, 4.4 Hz, 1H), 1.24 (s, 9H).

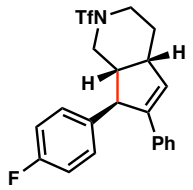
^{13}C NMR (101 MHz, d_6-DMSO, 90 ºC) δ 148.2, 143.9, 138.6, 135.1, 130.5, 127.7, 127.5, 127.3, 127.0, 126.7, 126.6, 125.8, 124.8, 119.6 (app q, *J* = 324.7 Hz), 53.0, 46.8, 45.8, 43.9, 39.4, 33.6, 30.7, 26.4.

^{19}F NMR (376 MHz, d_6-DMSO, 90 ºC) δ -75.0.

FT-IR (neat film NaCl): 2964, 1387, 1226, 1188, 1149, 762 cm $^{-1}$.

HR-MS (FD) m/z: [M•]+ Calculated for $C_{25}H_{28}F_3NO_2S$: 463.1793; Measured: 463.1797.

HPLC (ChiralPak ADH column) 98:02 (hex/*i*PrOH) 1mL/min; t_{major} (4.05 min), t_{minor} (4.95 min); 88% ee.



(4a*R*,7*R*,7a*R*)-7-(4-fluorophenyl)-6-phenyl-2-((trifluoromethyl)sulfonyl)-2,3,4,4a,7,7a-hexahydro-1*H*-cyclopenta[*c*]pyridine (213d)

Following General Procedure B: To a dram vial equipped with a stir bar was added **IDPi-211** (28.7 mg, 0.12 equiv, 0.012 mmol), cyclohexane (0.5 mL), and 2-allyl-1,1,1,3,3,3-hexaethyl-2-(triethylsilyl)trisilane (53.9 mg, 1.3 equiv, 0.13 mmol). To this solution was added vinyl tosylate **212d** (59.76 mg, 1.0 equiv, 0.1 mmol). The reaction was sealed with a Teflon cap and heated to 75 ºC for 96 hours, then the reaction was removed from the glovebox and a few drops of triethylamine were added to quench the reaction and diluted further with DCM. This homogeneous mixture was then plugged through silica gel with DCM/diethyl ether (1:1), concentrated *in vacuo*, and purified by flash column chromatography (5% diethyl ether in hexanes) to give insertion product **213d** as a white solid (24.3 mg, 57% yield). This material was determined by chiral HPLC to be 87% ee. [Note: this material could be recrystallized from hexanes to give material that was >99% enantiomeric excess.]

^{1}H NMR (400 MHz, d_6-DMSO, 90 ºC) δ 7.33 – 7.28 (m, 2H), 7.22 (dddd, *J* = 8.1, 6.5, 2.4, 1.2 Hz, 4H), 7.18 – 7.13 (m, 1H), 7.11 – 7.00 (m, 2H), 6.39 (dd, *J* = 2.5, 1.5 Hz, 1H), 4.11 (dt, *J* = 5.1, 1.7 Hz, 1H), 3.72 (dd, *J* = 13.3, 5.4 Hz, 1H), 3.57 – 3.37 (m, 3H), 3.21 – 3.14 (m, 1H), 2.37 (tt, *J* = 7.1, 5.2 Hz, 1H), 2.03 (dddd, *J* = 13.9, 7.6, 6.0, 4.2 Hz, 1H), 1.74 (dtd, *J* = 14.5, 7.4, 4.2 Hz, 1H).

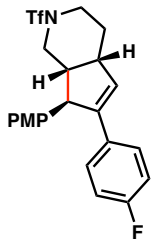
^{13}C NMR (101 MHz, d_6-DMSO, 90 ºC) δ 160.6 (d, J = 242.6 Hz), 143.7, 137.8 (d, J = 3.1 Hz), 134.8, 130.8, 128.9 (d, J = 8.0 Hz), 127.7, 126.7, 125.8, 119.5 (app q, J = 324.7 Hz), 114.9, 114.6, 52.5, 46.7, 45.6, 43.9, 26.4 (other signal not detected, likely under solvent peak).

^{19}F NMR (376 MHz, d_6-DMSO, 90 ºC) δ -75.0, -116.7

FT-IR (neat film NaCl): 2921, 1508, 1386, 1224, 1189, 1147, 1068, 758 cm^{-1}.

HR-MS (FD) m/z: [M•]+ Calculated for $C_{21}H_{19}F_4NO_2S$: 425.1073; Measured: 425.1062

HPLC (ChiralPak ADH column) 98:02 (hex/*i*PrOH) 1mL/min; t_{major} (6.42 min), t_{minor} (7.21 min); 87% ee.



(4a*R*,7*R*,7a*R*)-6-(4-fluorophenyl)-7-(4-methoxyphenyl)-2-((trifluoromethyl)sulfonyl)-2,3,4,4a,7,7a-hexahydro-1*H*-cyclopenta[*c*]pyridine (213e)

Following General Procedure B: To a dram vial equipped with a stir bar was added **IDPi-211** (28.7 mg, 0.12 equiv, 0.012 mmol), cyclohexane (1.0 mL), and 2-allyl-1,1,1,3,3,3-hexaethyl-2-(triethylsilyl)trisilane (53.9 mg, 1.3 equiv, 0.13 mmol). To this solution was added vinyl tosylate **212e** (63.0 mg, 1.0 equiv, 0.1 mmol). The reaction was sealed with a Teflon cap and heated to 65 ºC for 72 hours, then the reaction was removed from the glovebox and a few drops of triethylamine were added to quench the reaction and diluted further with DCM. This homogeneous mixture was then plugged through silica gel with

DCM/diethyl ether (1:1), concentrated *in vacuo*, and purified by flash column chromatography (10% diethyl ether in hexanes) to give insertion product **213e** as a sticky opaque solid (35.6 mg, 78% yield). This material was determined by chiral HPLC to be 91% ee.

^{1}H NMR (400 MHz, d_6-DMSO, 90 ºC) δ 7.36 – 7.30 (m, 2H), 7.12 – 7.08 (m, 2H), 7.03 – 6.98 (m, 2H), 6.85 – 6.80 (m, 2H), 6.33 (dd, *J* = 2.4, 1.5 Hz, 1H), 4.01 (dt, *J* = 5.3, 1.7 Hz, 1H), 3.71 (s, 3H), 3.70 –3.65 (m, 1H), 3.53 (ddt, *J* = 11.7, 7.6, 4.1 Hz, 1H), 3.42 (td, *J* = 12.8, 5.6 Hz, 2H), 3.17 – 3.10 (m, 1H), 2.34 (tt, *J* = 7.0, 5.3 Hz, 1H), 2.02 (dddd, *J* = 13.8, 7.5, 6.0, 4.0 Hz, 1H), 1.71 (dtd, *J* = 14.1, 7.6, 4.1 Hz, 1H).

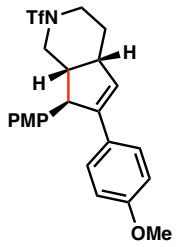
^{13}C NMR (101 MHz, d_6-DMSO, 90 ºC) δ 160.9 (d, *J* = 244.6 Hz), 157.7, 142.9, 133.4, 131.6 (d, *J* = 3.2 Hz), 130.37, 130.36, 128.1, 127.7 (d, *J* = 8.0 Hz), 119.5 (q, *J* = 324.8 Hz), 114.5, 114.3, 113.8, 54.6, 52.6, 46.9, 45.6, 43.9, 26.5 (other signal not detected, likely under solvent peak).

^{19}F NMR (376 MHz, d_6-DMSO, 90 ºC) δ -75.0, -115.0.

FT-IR (neat film NaCl): 2929, 1736, 1609, 1509, 1459, 1387, 1303, 1226, 1185, 1149, 1098, 1037, 987, 952, 831, 806 cm^{-1}.

HR-MS (FD) m/z: [M•]+ Calculated for $C_{22}H_{21}F_4NO_3S$: 455.1178; Measured: 455.1200.

HPLC (ChiralPak ADH column) 95:05 (hex/*i*PrOH) 1mL/min; t_{major} (6.74 min), t_{minor} (7.95 min); 91% ee.



(4a*R*,7*R*,7a*R*)-6,7-bis(4-methoxyphenyl)-2-((trifluoromethyl)sulfonyl)-2,3,4,4a,7,7a-hexahydro-1*H*-cyclopenta[*c*]pyridine (213f)

Following General Procedure B: To a dram vial equipped with a stir bar was added **IDPi-211** (28.7 mg, 0.12 equiv, 0.012 mmol), cyclohexane (1.0 mL), and 2-allyl-1,1,1,3,3,3-hexaethyl-2-(triethylsilyl)trisilane (53.9 mg, 1.3 equiv, 0.13 mmol). To this solution was added vinyl tosylate **212f** (64.0 mg, 1.0 equiv, 0.1 mmol). The reaction was sealed with a Teflon cap and heated to 65 ºC for 72 hours, then the reaction was removed from the glovebox and a few drops of triethylamine were added to quench the reaction and diluted further with DCM. This homogeneous mixture was then plugged through silica gel with DCM/diethyl ether (1:1), concentrated *in vacuo*, and purified by flash column chromatography (15% diethyl ether in hexanes) to give insertion product **213f** as a sticky white solid (28.1 mg, 60% yield). This material was determined by chiral HPLC to be 93% ee.

^{1}H NMR (400 MHz, d_6-DMSO, 90 ºC) δ 7.26 – 7.21 (m, 2H), 7.12 – 7.08 (m, 2H), 6.85 – 6.80 (m, 2H), 6.80 – 6.76 (m, 2H), 6.21 (t, *J* = 1.9 Hz, 1H), 3.97 (d, *J* = 4.9 Hz, 1H), 3.71 (d, *J* = 3.0 Hz, 6H), 3.67 (m, 1H), 3.53 – 3.35 (m, 3H), 3.13 (d, *J* = 6.9 Hz, 1H), 2.31 (q, *J* = 6.4 Hz, 1H), 2.01 (ddd, *J* = 13.9, 6.8, 2.4 Hz, 1H), 1.71 (ddt, *J* = 10.3, 7.4, 3.2 Hz, 1H).

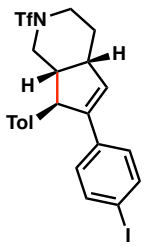
^{13}C NMR (101 MHz, d_6-DMSO, 90 ºC) δ 158.3, 157.6, 143.5, 133.8, 128.1, 127.7, 127.0, 119.5 (q, *J* = 324.8 Hz), 113.8, 113.4, 54.7, 54.6, 52.7, 46.8, 45.7, 43.9, 39.2, 26.5.

^{19}F NMR (376 MHz, d_6-DMSO, 90 ºC) δ -75.0

FT-IR (neat film NaCl): 2926, 1607, 1511, 1463, 1386, 1249, 1226, 1180, 1148, 1065, 1037, 986, 952, 831 cm $^{-1}$.

HR-MS (ESI) m/z: $[M+NH_4]+$ Calculated for $C_{23}H_{28}F_3N_2O_4S$: 485.1716; Measured: 485.1711.

HPLC (ChiralPak ADH column) 90:10 (hex/*i*PrOH) 1mL/min; t_{major} (6.90 min), t_{minor} (8.24 min); 93% ee.



(4a*R*,7*R*,7a*R*)-6-(4-iodophenyl)-7-(*p*-tolyl)-2-((trifluoromethyl)sulfonyl)-2,3,4,4a,7,7a-hexahydro-1*H*-cyclopenta[*c*]pyridine (213g)

Following General Procedure B: To a dram vial equipped with a stir bar was added **IDPi-211** (28.7 mg, 0.12 equiv, 0.012 mmol), cyclohexane (0.5 mL), and 2-allyl-1,1,1,3,3,3-hexaethyl-2-(triethylsilyl)trisilane (53.9 mg, 1.3 equiv, 0.13 mmol). To this solution was added vinyl tosylate **212g** (72.0 mg, 1.0 equiv, 0.1 mmol). The reaction was sealed with a Teflon cap and heated to 65 ºC for 72 hours, then the reaction was removed from the glovebox and a few drops of triethylamine were added to quench the reaction and diluted further with DCM. This homogeneous mixture was then plugged through silica gel with DCM/diethyl ether (1:1), concentrated *in vacuo*, and purified by flash column

chromatography (5% diethyl ether in hexanes) to give insertion product **213g** as a clear oil (29.8 mg, 54% yield). This material was determined by chiral HPLC to be 90% ee.

^{1}H NMR (400 MHz, d_6-DMSO, 90 ºC) δ 7.64 – 7.47 (m, 2H), 7.12 – 7.08 (m, 2H), 7.06 (s, 4H), 6.42 (dd, *J* = 2.5, 1.5 Hz, 1H), 4.02 (dt, *J* = 5.4, 1.7 Hz, 1H), 3.67 (dd, *J* = 13.3, 5.3 Hz, 1H), 3.53 (ddd, *J* = 11.9, 7.4, 4.2 Hz, 1H), 3.47 – 3.36 (m, 2H), 3.16 – 3.10 (m, 1H), 2.34 (tt, *J* = 7.0, 5.3 Hz, 1H), 2.24 (s, 3H), 2.02 (dddd, *J* = 13.8, 7.4, 6.0, 4.0 Hz, 1H), 1.70 (dtd, *J* = 14.1, 7.8, 4.1 Hz, 1H).

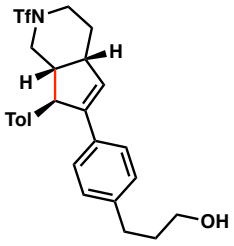
^{13}C NMR (101 MHz, d_6-DMSO, 90 ºC) δ 142.9, 138.4, 136.5, 135.1, 134.7, 131.7, 128.7, 127.9, 127.0, 119.5 (app q, *J* = 324.7 Hz), 92.1, 52.7, 46.9, 45.5, 43.9, 39.45, 26.4, 20.0.

^{19}F NMR (376 MHz, d_6-DMSO, 90 ºC) δ -74.9

FT-IR (neat film NaCl): 2932, 1738, 1514, 1486, 1385, 1225, 1187, 1002, 952, 814 cm $^{-1}$.

HR-MS (ESI) m/z: [M+Na]+ Calculated for $C_{22}H_{21}F_3INNaO_2S$: 570.0182; Measured: 570.0191.

HPLC (ChiralPak ADH column) 98:02 (hex/*i*PrOH) 1mL/min; t_{major} (6.94 min), t_{minor} (9.92 min); 90% ee.



3-(4-((4a*R*,7*R*,7a*R*)-7-(*p*-tolyl)-2-((trifluoromethyl)sulfonyl)-2,3,4,4a,7,7a-hexahydro-1*H*-cyclopenta[*c*]pyridin-6-yl)phenyl)propan-1-ol (213h)

Following a slightly modified version of General Procedure A: To a dram vial equipped with a stir bar was added **IDPi-211** (28.7 mg, 0.12 equiv, 0.012 mmol), cyclohexane (0.5 mL), and 2-allyl-1,1,1,3,3,3-hexaethyl-2-(triethylsilyl)trisilane (95.4 mg, 2.3 equiv, 0.23 mmol). To this solution was added vinyl tosylate **212h** (65.2 mg, 1.0 equiv, 0.1 mmol). The reaction was sealed with a Teflon cap and heated to 65 ºC for 72 hours. After this time, the reaction was removed from the glovebox and to the reaction vial was added 1 mL of a freshly prepared solution of TBAF•$(H_2O)_3$ in THF (0.05M) at room temperature and allowed to stir overnight. The next morning, saturated aqueous ammonium chloride was added to the reaction vial (~2 mL) then the mixture was extracted with ethyl acetate three times. The combined organics were dried over Na_2SO_4, filtered, concentrated *in vacuo*, then purified *via* flash chromatography (1% → 2% diethyl ether in DCM) to obtain free alcohol **213h** as a white solid (30.7 mg, 64% yield). This material was determined by chiral HPLC to be in 87% ee.

^{1}H NMR (400 MHz, d_6-DMSO, 90 ºC) δ 7.25 – 7.15 (m, 2H), 7.12 – 6.98 (m, 6H), 6.30 (dd, *J* = 2.4, 1.5 Hz, 1H), 4.00 (dt, *J* = 5.0, 1.7 Hz, 1H), 3.69 (dd, *J* = 13.3, 5.4 Hz, 1H), 3.56 – 3.32 (m, 5H), 3.15 (q, *J* = 6.9 Hz, 1H), 2.57 – 2.52 (m, 2H), 2.33 (tt, *J* = 7.2, 5.2 Hz, 1H), 2.24 (s, 3H), 2.02 (dddd, *J* = 13.9, 7.6, 6.0, 4.2 Hz, 1H), 1.79 – 1.62 (m, 3H).

^{13}C NMR (101 MHz, d_6-DMSO, 90 ºC) δ 143.7, 140.8, 138.8, 134.9, 132.3, 129.4, 128.6, 127.5, 126.9, 125.6, 119.5 (q, *J* = 324.8 Hz), 59.7, 53.0, 46.8, 45.6, 43.8, 33.4, 30.8, 26.4, 19.9.

^{19}F NMR (376 MHz, d_6-DMSO, 90 ºC) δ -74.9.

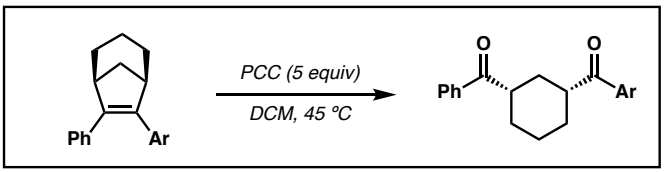
FT-IR (neat film NaCl): 3366 (br s), 2919, 2859, 1732, 1653, 1561, 1512, 1447, 1386, 1269, 1226, 1186, 1148, 1065, 1045, 984, 952, 819, 735, 606.

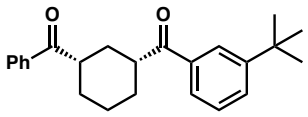
HR-MS (ESI) m/z: [M+H]+ Calculated for $C_{25}H_{29}F_3NO_3S$: 480.1815; Measured: 480.1809.

HPLC (ChiralPak ADH column) 90:10 (hex/*i*PrOH) 1mL/min; t_{major} (7.86 min), t_{minor} (9.69 min); 87% ee.

4.5.5 Product Manipulation

Oxidative cleavage of bicyclo[3.2.1]octenes:





(3-benzoylcyclohexyl)(3-(*tert*-butyl)phenyl)methanone (210a)

Following a similar reported procedure[24]: To a dram vial equipped with a stir bar was added bicycle **205a** (16.2 mg, 1.0 equiv, 0.0512 mmol) and DCM (1.0 mL). To this solution was added PCC (55.2 mg, 5.0 equiv, 0.256 mmol). The reaction was sealed with a Teflon cap and heated to 45 ºC for 18 hours. The reaction was then cooled to room temperature, diluted with DCM, plugged through silica gel with DCM, and concentrated *in vacuo.* The crude material was purified by flash column chromatography (10% diethyl ether in hexanes) to give diketone **210a** as a viscous oil (13.4 mg, 75% yield). The relative stereochemistry was assigned based on NOESY NMR. This material was determined by chiral HPLC to be 77% ee (100% es).

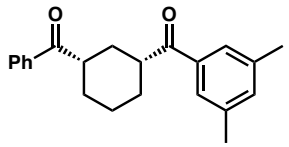
^{1}H NMR (400 MHz, C_6D_6) δ 8.27 (t, *J* = 1.9 Hz, 1H), 7.91 – 7.84 (m, 2H), 7.70 (ddd, *J* = 7.7, 1.7, 1.1 Hz, 1H), 7.36 (ddd, *J* = 7.8, 2.1, 1.1 Hz, 1H), 7.16 – 7.06 (m, 4H), 3.15 (tt, *J* = 11.8, 3.5 Hz, 1H), 3.05 (tt, *J* = 11.9, 3.5 Hz, 1H), 2.12 (ddq, *J* = 11.8, 3.6, 1.8 Hz, 1H), 2.04 (dt, *J* = 13.6, 11.7 Hz, 1H), 1.84 (dtt, *J* = 11.7, 3.4, 1.8 Hz, 1H), 1.76 (dtt, *J* = 11.7, 3.3, 1.8 Hz, 1H), 1.61 (dt, *J* = 13.1, 3.3 Hz, 1H), 1.53 – 1.45 (m, 2H), 1.24 – 1.20 (m, 1H), 1.19 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.0, 202.7, 152.0, 136.3, 136.0, 133.1, 130.3, 128.8, 128.4, 128.3, 125.6, 125.2, 45.2, 45.1, 35.0, 31.9, 31.4, 29.2, 29.1, 25.6.

FT-IR (neat film NaCl): 2926, 2852, 1680, 1596, 1447, 1367, 1252, 1205, 1179, 1007, 960, 697 cm $^{-1}$.

HR-MS (ESI) m/z: [M+Na]+ Calculated for $C_{24}H_{28}NaO_2$: 371.1982; Measured: 371.1990.

HPLC (CHIRALCEL ODH column) 95:5 (hex/*i*PrOH) 1.0 mL/min; t_{major} (9.74 min), t_{minor} (11.75 min); 77% ee (100% es)



***(*3-benzoylcyclohexyl)(3,5-dimethylphenyl)methanone (210b)**

Following a similar reported procedure[24]: To a dram vial equipped with a stir bar was added bicycle **205b** (16.2 mg, 1.0 equiv, 0.0512 mmol) and DCM (1.0 mL). To this solution was added PCC (55.2 mg, 5.0 equiv, 0.256 mmol). The reaction was sealed with a Teflon cap and heated to 45 ºC for 18 hours. The reaction was then cooled to room temperature, diluted with DCM, plugged through silica gel with DCM, and concentrated *in vacuo.* The crude material was purified by flash column chromatography (10% diethyl ether in hexanes) to

give diketone **210b** as a viscous oil (13.4 mg, 75% yield). The relative stereochemistry was assigned based on NOESY NMR. This material was determined by chiral HPLC to be 74% ee (101% es).

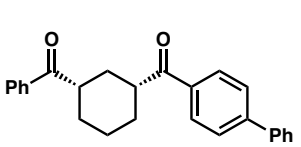
^{1}H NMR (400 MHz, C_6D_6) δ 7.89 – 7.85 (m, 2H), 7.65 (d, *J* = 1.7 Hz, 2H), 7.15 – 7.05 (m, 3H), 6.85 (t, *J* = 1.5 Hz, 1H), 3.17 – 3.09 (m, 1H), 3.04 (tt, *J* = 11.8, 3.5 Hz, 1H), 2.11 (dt, *J* = 5.1, 2.4 Hz, 1H), 2.09 (s, 6H), 1.86 (dtt, *J* = 11.6, 3.4, 1.7 Hz, 1H), 1.79 – 1.74 (m, 1H), 1.63 – 1.58 (m, 1H), 1.56 – 1.40 (m, 3H), 1.19 (dt, *J* = 13.1, 3.6 Hz, 1H).

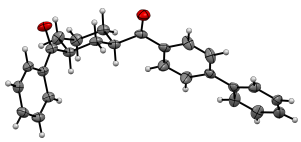
^{13}C NMR (101 MHz, $CDCl_3$) δ 203.2, 202.7, 138.4, 136.5, 136.3, 134.7, 133.1, 128.8, 128.4, 126.1, 45.20, 45.18, 31.8, 29.9, 29.2, 29.1, 25.6, 21.4.

FT-IR (neat film NaCl): 2921, 1677, 1598, 1301, 696 cm $^{-1}$.

HR-MS (ESI) m/z: [M+Na]+ Calculated for $C_{22}H_{24}NaO_2$: 343.1669; Measured: 343.1682.

HPLC (ChiralPak ADH column) 90:10 (hex/*i*PrOH) 1.0mL/min; t_{minor} (8.42 min), t_{major} (10.29 min); 74% ee (101% es).





(3-([1,1'-biphenyl]-4-carbonyl)cyclohexyl)(phenyl)methanone (210c)

Following a similar reported procedure[24]: To a dram vial equipped with a stir bar was added bicycle **205c** (17.7 mg, 1.0 equiv, 0.0526 mmol) and DCM (1.0 mL). To this solution was added PCC (56.7 mg, 5.0 equiv, 0.263 mmol). The reaction was sealed with a Teflon cap and heated to 45 ºC for 18 hours. The reaction was then cooled to rt, diluted with DCM, plugged through silica gel with DCM, and concentrated *in vacuo.* The crude material was purified by flash column chromatography (10% diethyl ether in hexanes) to give **210c** as a

white solid (13.0 mg, 67% yield). The relative and absolute stereochemistry was assigned based on X-ray crystallographic analysis. This material was determined by chiral HPLC to be 72% ee (99% es). Recrystallization from *n*-hexane/DCM affords highly enantioenriched material (>99% ee).

^{1}H NMR (400 MHz, C_6D_6) δ 7.99 – 7.94 (m, 2H), 7.94 – 7.85 (m, 2H), 7.46 – 7.40 (m, 4H), 7.25 – 7.20 (m, 2H), 7.17 (t, *J* = 1.4 Hz, 1H), 7.15 – 7.06 (m, 3H), 3.14 – 3.02 (m, 2H), 2.15 – 2.06 (m, 2H), 1.86 – 1.76 (m, 2H), 1.65 – 1.60 (m, 1H), 1.52 – 1.44 (m, 2H), 1.24 – 1.20 (m, 1H).

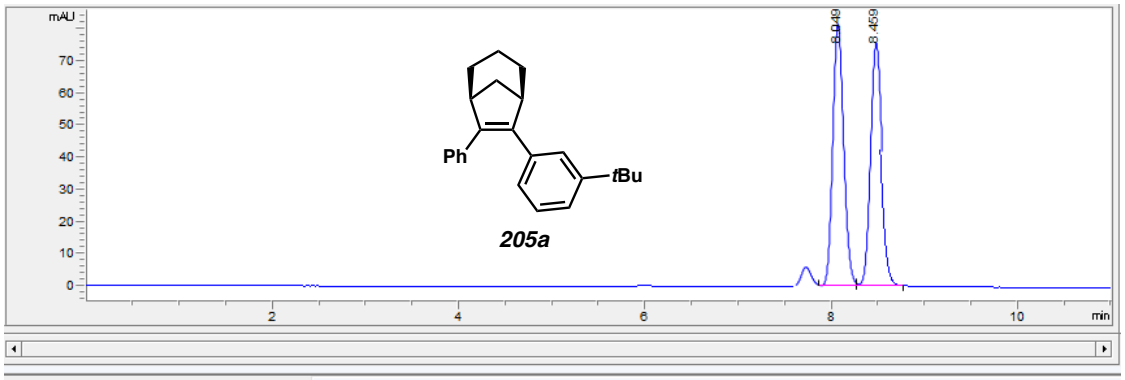
^{13}C NMR (101 MHz, $CDCl_3$) δ 202.7, 202.3, 145.8, 140.0, 136.26, 134.9, 133.1, 129.1, 129.0, 128.8, 128.4, 128.3, 127.5, 127.4, 45.2, 45.1, 31.7, 29.3, 29.2, 25.7.

FT-IR (neat film NaCl): 2921, 2852, 1678, 1602, 1446, 1405, 1372, 1260, 1210, 1001, 768, 744, 696, 661, 607 cm $^{-1}$.

HR-MS (ESI) m/z: [M+Na]+ Calculated for $C_{26}H_{24}NaO_2$: 391.1669; Measured: 391.1671.

HPLC (ChiralPak ADH column) 80:20 (hex/*i*PrOH) 1.0mL/min; t_{major} (15.56 min), t_{minor} (17.31 min); 72% ee (99% es).

4.5.6 Chiral HPLC Traces of Enantioenriched Products



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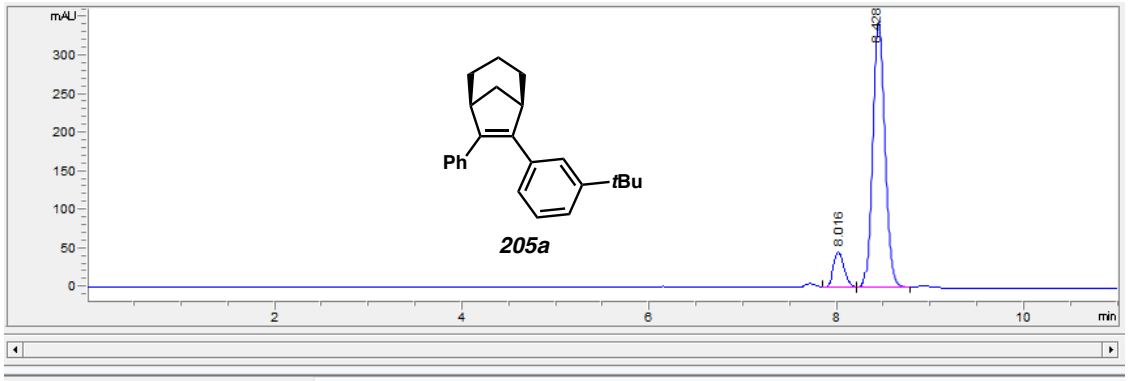
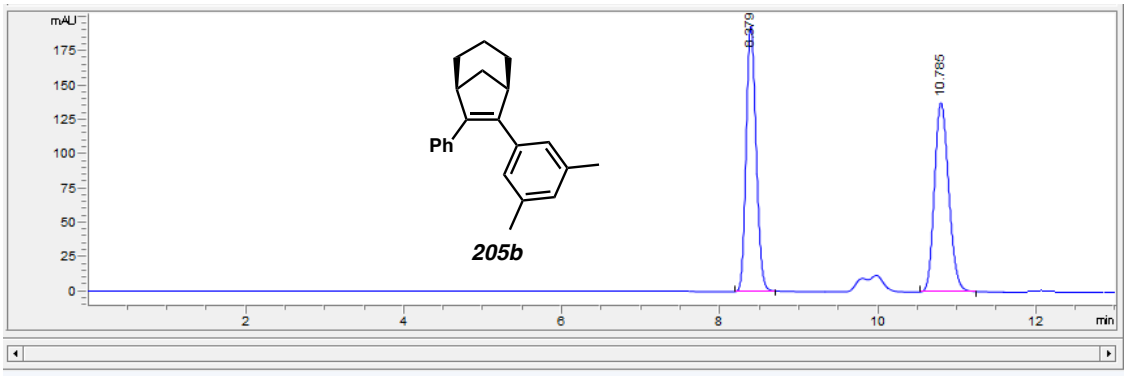
2	8.459	672.2	75.9	0.1373	50.131	0.854



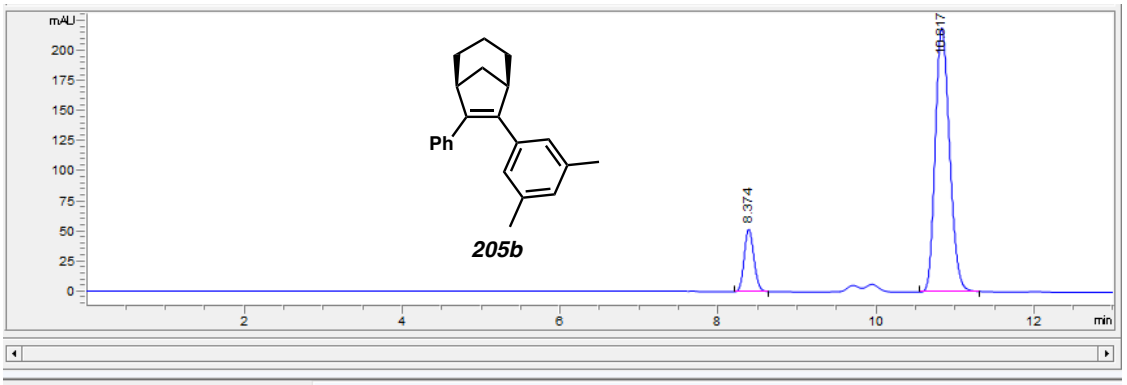
File Information	
LC-File	CGW-22-0133-1.D
File Path	C:\Chem32\1\Data\CGW
Date	30-May-22, 18:30:42
Sample	CGW-22-0133-1
Sample Info	
Barcode	
Operator	SYSTEM
Method	ODH0.1to99.9IPAHEX10
Reference	C:\Chem32\1\Data\CGW

#	Time	Area	Height	Width	Area%	Symmetry
1	8.016	373.7	46	0.1259	10.787	0.878
2	8.428	3090.9	344.2	0.1398	89.213	0.844



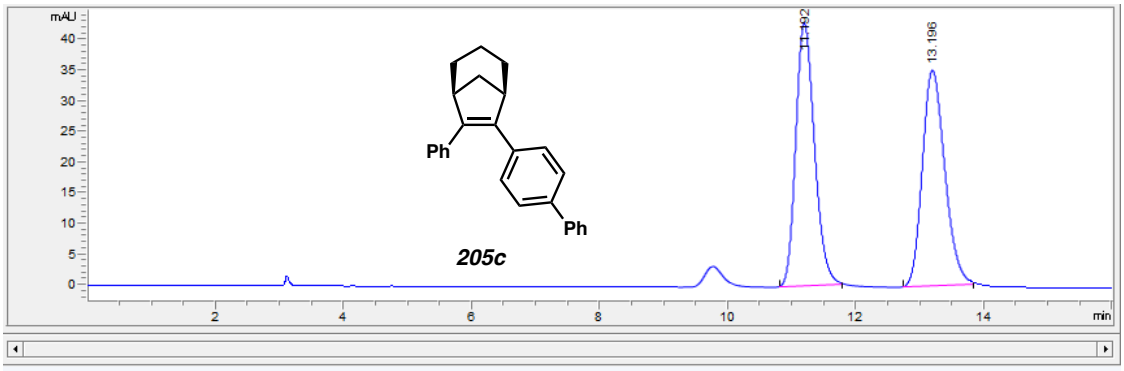
File Information	
LC-File	CGW-22-0144-2--011.D
File Path	C:\Chem32\1\Data\CGW
Date	26-Jun-22, 18:06:36
Sample	CGW-22-0144-2
Sample Info	
Barcode	
Operator	SYSTEM
Method	ODH0.1to99.9IPAHEX12
Reference	C:\Chem32\1\Data\CGW

#	Time	Area	Height	Width	Area%	Symmetry
1	8.379	1694.1	192.7	0.1366	49.495	0.828
2	10.785	1728.6	137.7	0.1965	50.505	0.804



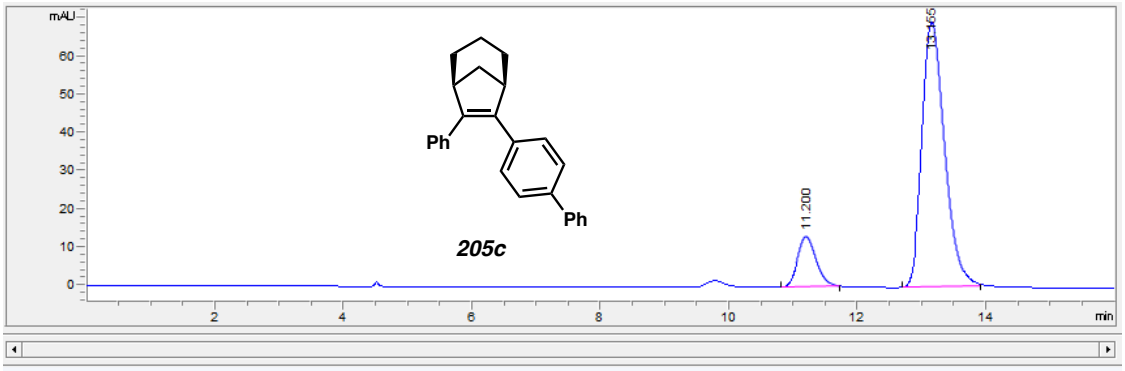
File Information	
LC-File	CGW-22-0137-2.D
File Path	C:\Chem32\1\Data\CGW
Date	06-Jun-22, 17:21:37
Sample	CGW-22-0137-2
Sample Info	
Barcode	
Operator	SYSTEM
Method	ODH0.1to99.9IPAHEX12
Reference	C:\Chem32\1\Data\CGW

#	Time	Area	Height	Width	Area%	Symmetry
1	8.374	444.8	52.2	0.1323	13.745	0.862
2	10.817	2791.5	220.3	0.1968	86.255	0.783



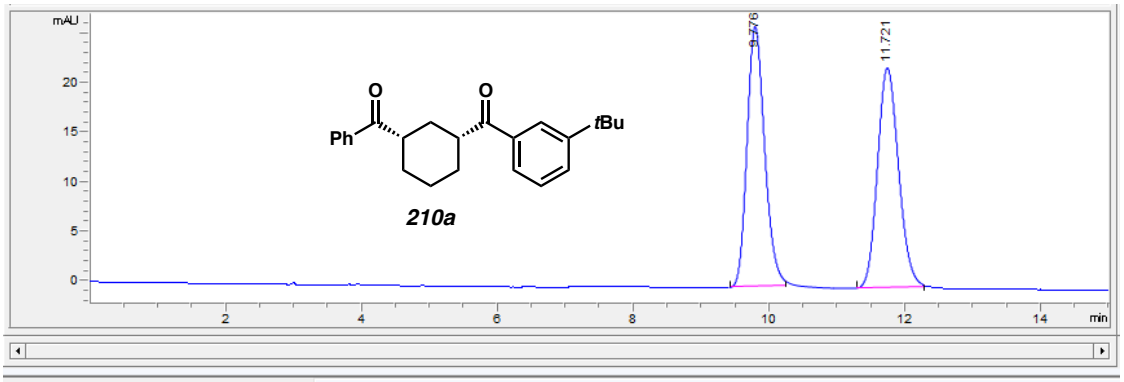
File Information	
LC-File	OnlineEdited--005.D
File Path	C:\Chem32\1\Data\CGW
Date	01-Jul-22, 13:26:18
Sample	CGW-22-0144-3-rac2
Sample Info	
Barcode	
Operator	SYSTEM
Method	ODH0.1to99.9IPAHEX16
Reference	C:\Chem32\1\Data\CGW

#	Time	Area	Height	Width	Area%	Symmetry
1	11.192	873	42.9	0.3164	50.359	0.772
2	13.196	860.5	35.1	0.378	49.641	0.769



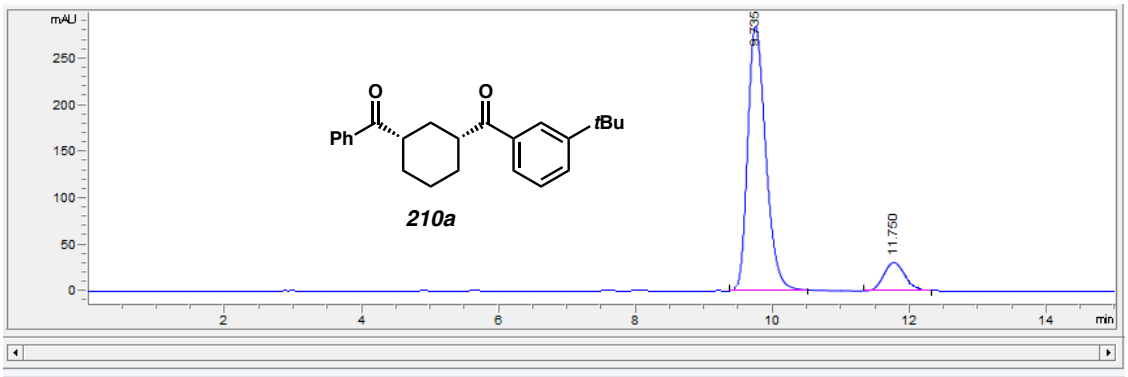
File Information	
LC-File	CGW-22-0145-3.D
File Path	C:\Chem32\1\Data\CGW
Date	01-Jul-22, 11:30:28
Sample	CGW-22-0145-3
Sample Info	
Barcode	
Operator	SYSTEM
Method	ODH0.1to99.9IPAHEX16
Reference	C:\Chem32\1\Data\CGW

#	Time	Area	Height	Width	Area%	Symmetry
1	11.2	272.6	13.2	0.3213	13.701	0.804
2	13.155	1717	69.2	0.3815	86.299	0.721



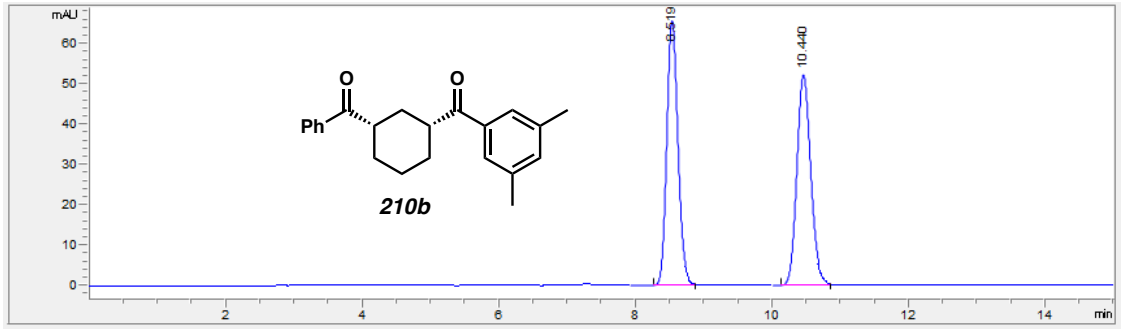
File Information	
LC-File	CGW-22-0143-1-tbutylra
File Path	C:\Chem32\1\Data\CGW
Date	28-Jun-22, 13:19:48
Sample	CGW-22-0143-1-tbutylra
Sample Info	
Barcode	
Operator	SYSTEM
Method	ODH0595IPAHEX15min1r
Reference	C:\Chem32\1\Data\CGW

#	Time	Area	Height	Width	Area%	Symmetry
1	9.776	471.9	26.2	0.2781	49.627	0.797
2	11.721	479	22.1	0.3383	50.373	0.836



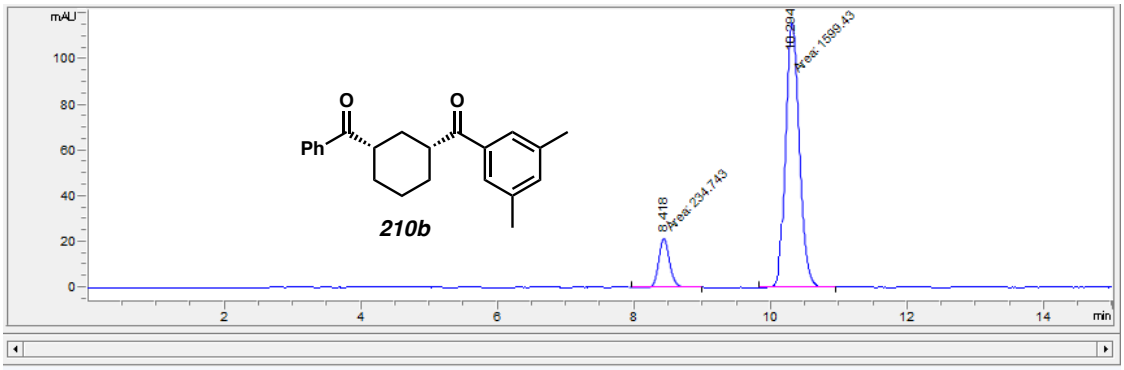
File Information	
LC-File	CGW-22-0143-1-tbutyl-2
File Path	C:\Chem32\1\Data\CGW
Date	27-Jun-22, 19:43:53
Sample	CGW-22-0143-1-tbutyl-2
Sample Info	
Barcode	
Operator	SYSTEM
Method	ODH0595IPAHEX15min1r
Reference	C:\Chem32\1\Data\CGW

#	Time	Area	Height	Width	Area%	Symmetry
1	9.735	5213.1	284.7	0.2826	88.587	0.715
2	11.75	671.7	30.6	0.3407	11.413	0.834



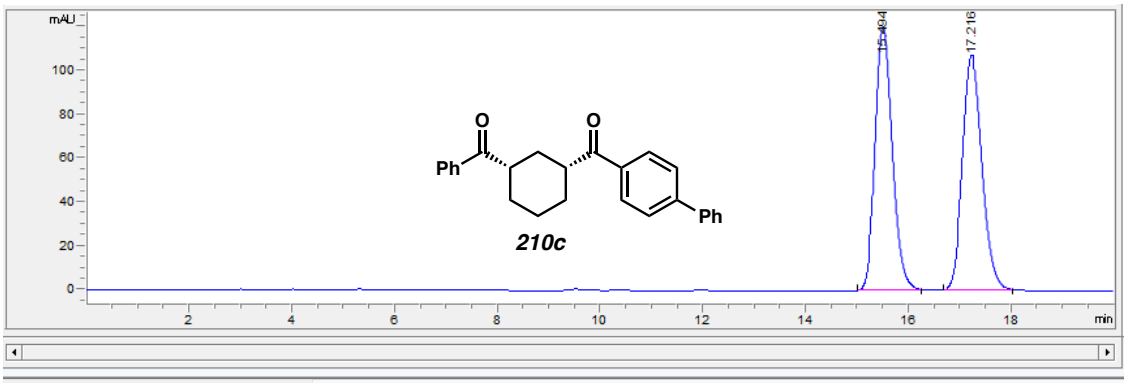
File Information	
LC-File	CGW-diketone-rac-8.D
File Path	C:\Chem32\1\Data\BW\(
Date	25-May-22, 08:43:11
Sample	CGW-diketone-rac-8
Sample Info	
Barcode	
Operator	SYSTEM
Method	ADH1090IPAHEX15min1r
Reference	C:\Chem32\1\Data\BW\(

#	Time	Area	Height	Width	Area%	Symmetry
1	8.519	741.1	65.5	0.175	49.876	0.836
2	10.44	744.8	52.1	0.2207	50.124	0.845



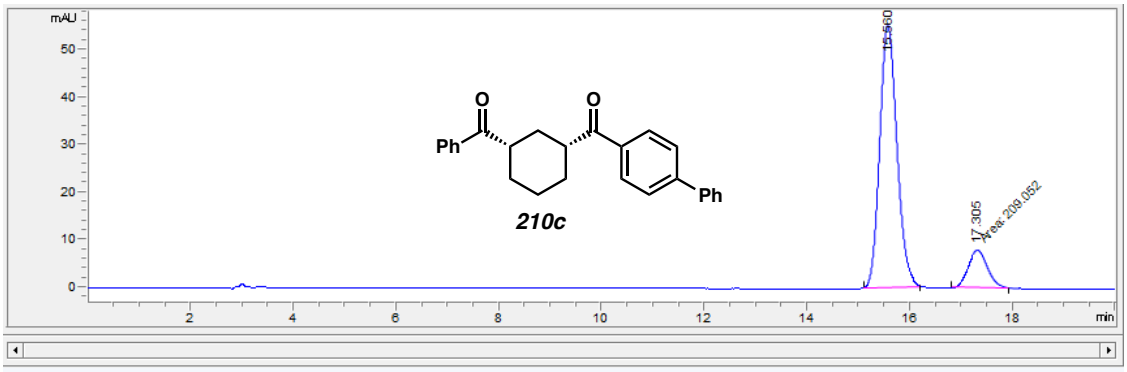
File Information	
LC-File	OnlineEdited--014.D
File Path	C:\Chem32\1\Data\CGW
Date	24-Jun-22, 16:04:21
Sample	CGW-22-0143-2-again
Sample Info	
Barcode	
Operator	SYSTEM
Method	ADH1090IPAHEX15min1r
Reference	C:\Chem32\1\Data\CGW

#	Time	Area	Height	Width	Area%	Symmetry
1	8.418	234.7	21.4	0.1826	12.798	0.866
2	10.294	1599.4	115.8	0.2302	87.202	0.842



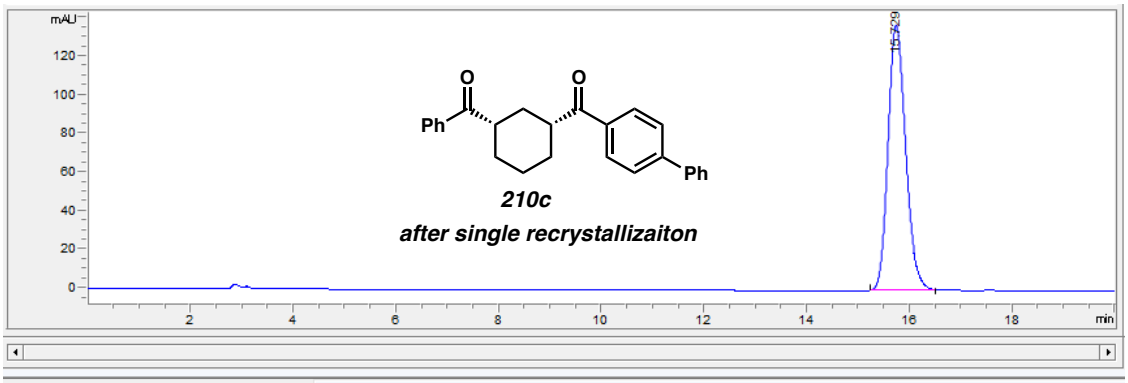
File Information	
LC-File	CGW-22-0143-3-rac2.D
File Path	C:\Chem32\1\Data\CGW
Date	02-Jul-22, 13:44:22
Sample	CGW-22-0143-3-rac2
Sample Info	
Barcode	
Operator	SYSTEM
Method	ADH2080IPAHEX20min1.
Reference	C:\Chem32\1\Data\CGW

#	Time	Area	Height	Width	Area%	Symmetry
1	15.494	2832.2	120.7	0.3637	50.056	0.802
2	17.216	2825.9	107.4	0.4079	49.944	0.8



File Information	
LC-File	CGW-22-0143-3-rerun2.
File Path	C:\Chem32\1\Data\CGW
Date	02-Jul-22, 15:32:59
Sample	CGW-22-0143-3-rerun2
Sample Info	
Barcode	
Operator	SYSTEM
Method	ADH2080IPAHEX20min1.
Reference	C:\Chem32\1\Data\CGW

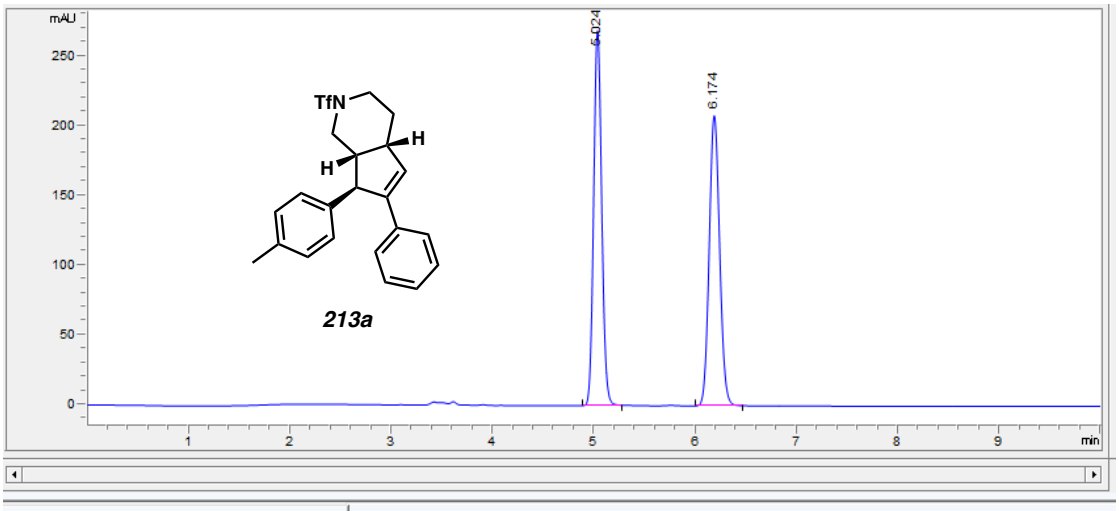
#	Time	Area	Height	Width	Area%	Symmetry
1	15.56	1300.1	55.5	0.3623	86.148	0.832
2	17.305	209.1	8	0.4328	13.852	0.873



File Information	
LC-File	CGW-22-0143-3-recryst.
File Path	C:\Chem32\1\Data\CGW
Date	08-Jul-22, 09:49:05
Sample	CGW-22-0143-3-recryst
Sample Info	
Barcode	
Operator	SYSTEM
Method	ADH2080IPAHEX20min1.
Reference	C:\Chem32\1\Data\CGW

#	Time	Area	Height	Width	Area%	Symmetry
1	15.729	3274.9	137	0.37	100.000	0.798

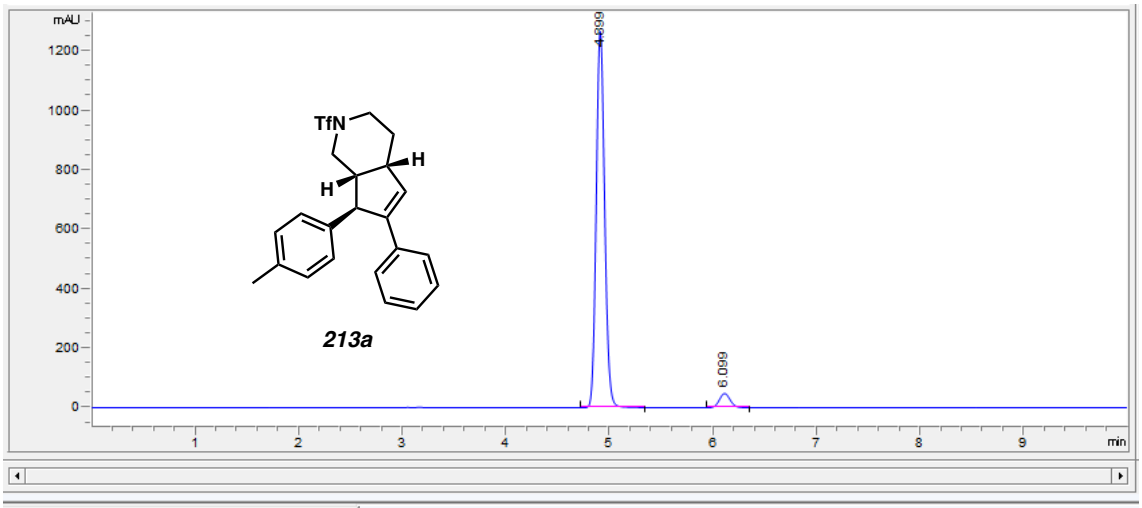
**Recrystallized once from hexanes.*



213a

File Information	
LC-File	bw-21-0235D.D
File Path	C:\Chem32\1\Data\BW\BW-21
Date	13-Aug-21, 16:16:49
Sample	bw-21-0235D

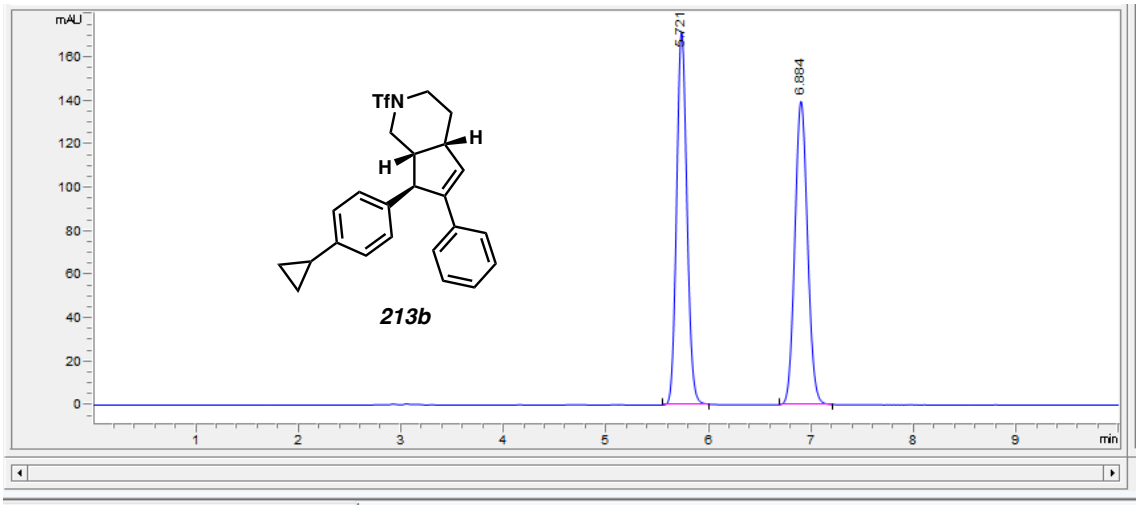
#	Time	Area	Height	Width	Area%	Symmetry
1	5.024	1485.4	269.2	0.0864	49.997	0.886
2	6.174	1485.5	208.5	0.1111	50.003	0.9



213a

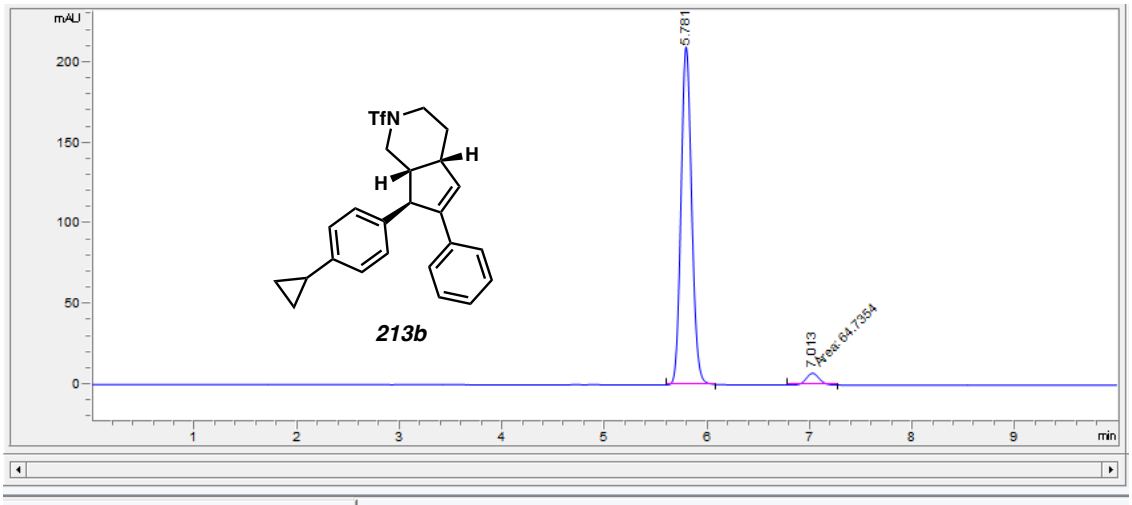
File Information	
LC-File	SKN-22-0024-12.D
File Path	C:\Chem32\1\Data\Sepand\SK
Date	20-Feb-22, 12:56:27
Sample	SKN-22-0024-12

#	Time	Area	Height	Width	Area%	Symmetry
1	4.899	7140	1265.8	0.0868	95.345	0.861
2	6.099	348.6	47.7	0.1132	4.655	0.903



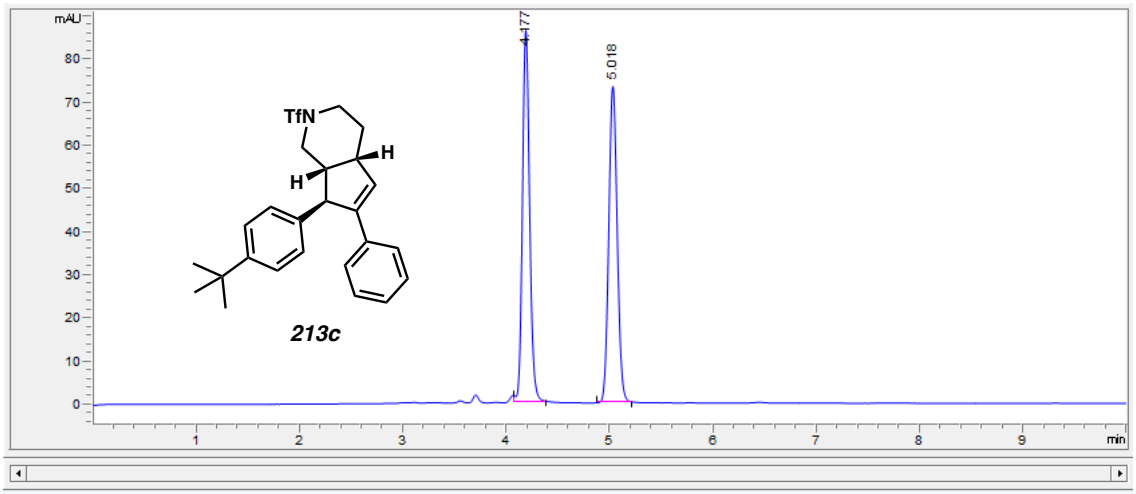
File Information	
LC-File	CGW-22-0005-2.D
File Path	C:\Chem32\1\Data\CGW\CGW
Date	12-Jan-22, 11:30:38
Sample	CGW-22-0005-2

#	Time	Area	Height	Width	Area%	Symmetry
1	5.721	1202.4	171.9	0.1086	49.964	0.877
2	6.884	1204.2	139.7	0.1345	50.036	0.905



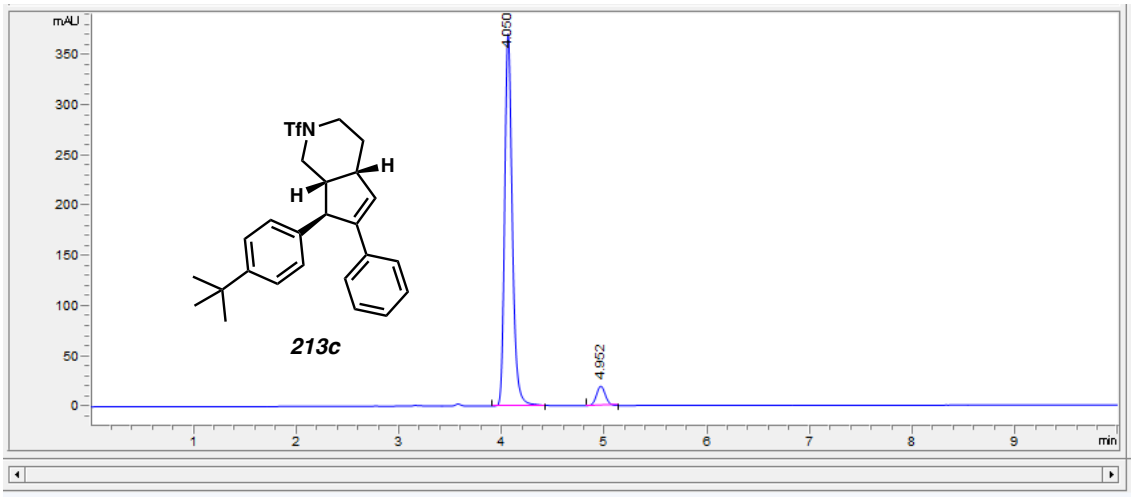
File Information	
LC-File	CGW-22-0065-1.D
File Path	C:\Chem32\1\Data\CGW\CGW
Date	28-Feb-22, 18:29:39
Sample	CGW-22-0065-1

#	Time	Area	Height	Width	Area%	Symmetry
1	5.781	1515.1	209.8	0.1122	95.902	0.87
2	7.013	64.7	7.3	0.1482	4.098	0.932



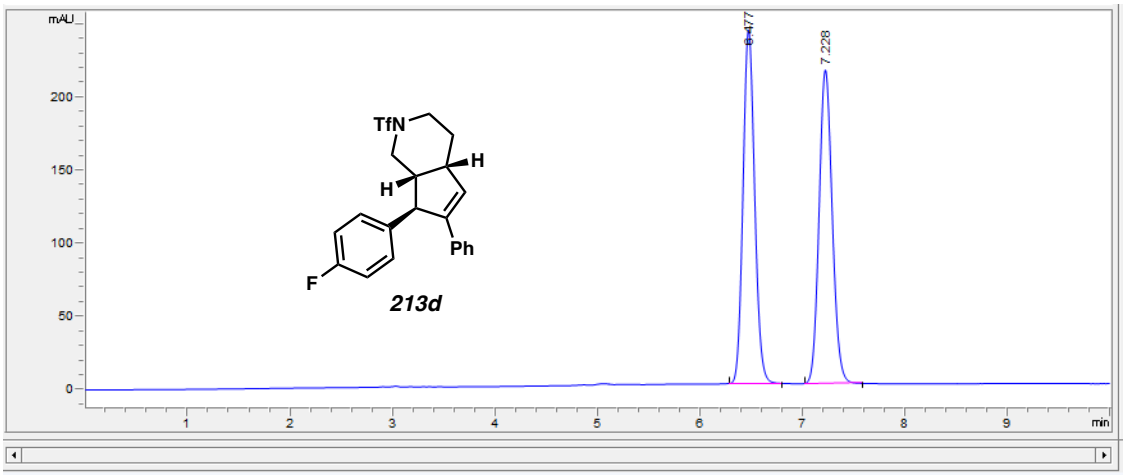
File Information	
LC-File	CGW-21-0253-2.D
File Path	C:\Chem32\1\Data\CGW\CGW
Date	02-Sep-21, 20:37:00
Sample	CGW-21-0253-2

#	Time	Area	Height	Width	Area%	Symmetry
1	4.177	416.4	86.3	0.0743	49.999	0.833
2	5.018	416.5	73.3	0.0883	50.001	0.907



File Information	
LC-File	CGW-22-0076-hplcround2-2.D
File Path	C:\Chem32\1\Data\CGW\CGW
Date	13-Mar-22, 18:40:49
Sample	CGW-22-0076-hplcround2-2

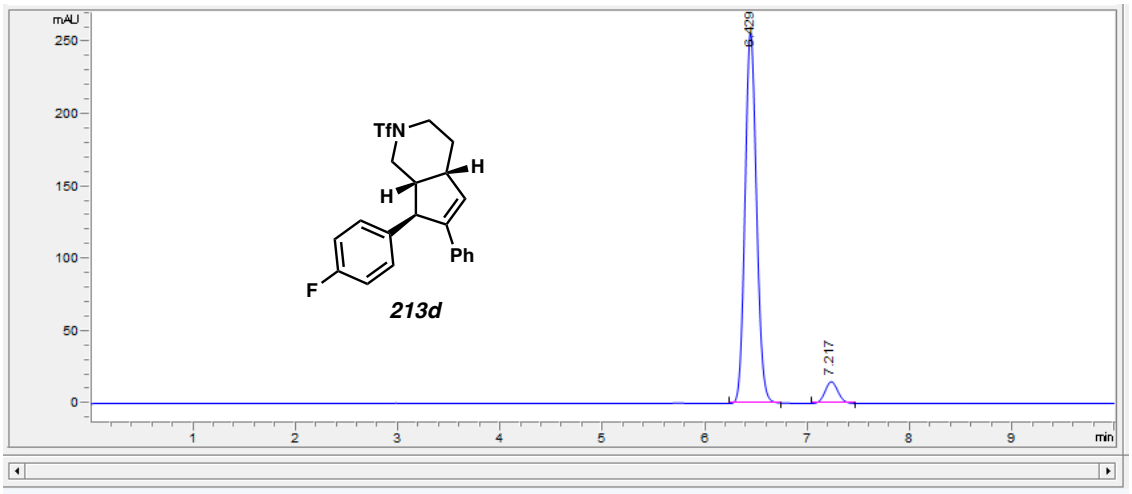
#	Time	Area	Height	Width	Area%	Symmetry
1	4.05	1920.1	371.5	0.0783	94.220	0.758
2	4.952	117.8	19.4	0.0938	5.780	0.904



213d

File Information	
LC-File	CGW-22-0134-3.D
File Path	C:\Chem32\1\Data\CGW\CGW-3
Date	29-May-22, 13:35:42
Sample	CGW-22-0134-3

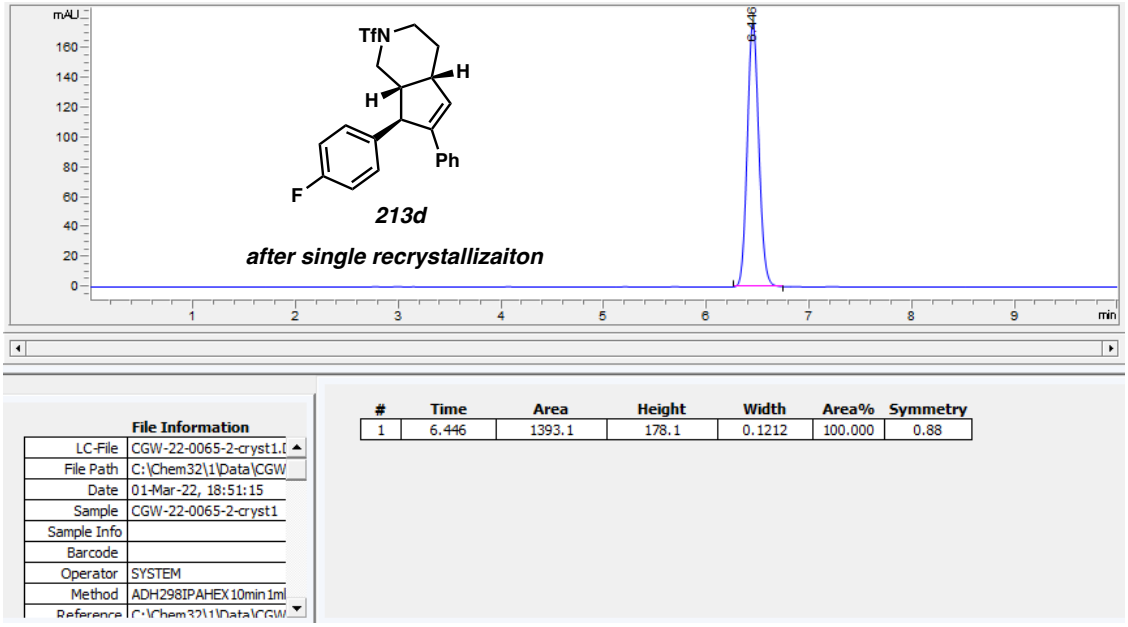
#	Time	Area	Height	Width	Area%	Symmetry
1	6.477	1911.9	241.7	0.1223	49.988	0.869
2	7.228	1912.8	214.2	0.1382	50.012	0.874



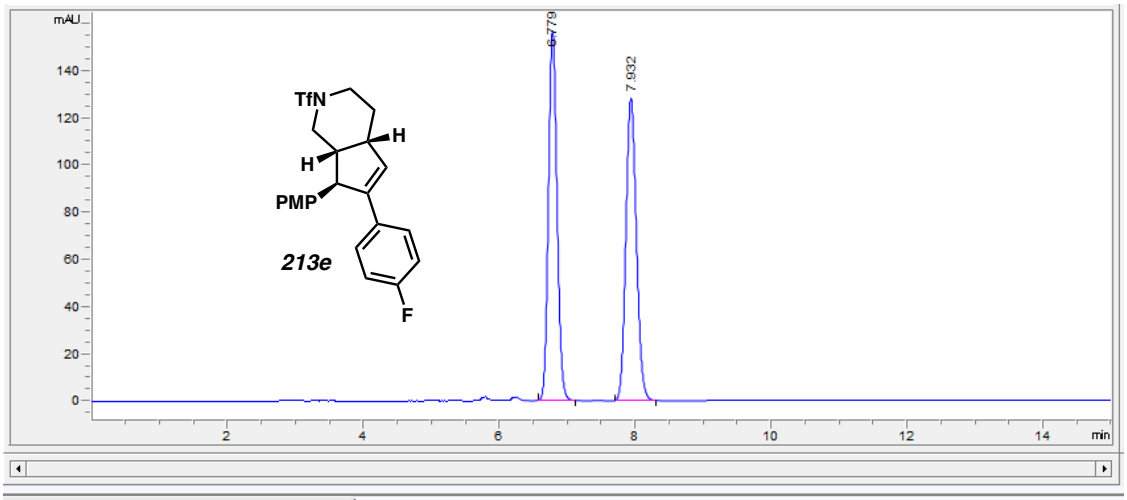
213d

File Information	
LC-File	CGW-22-0065-2.D
File Path	C:\Chem32\1\Data\CGW\CGW
Date	28-Feb-22, 19:06:16
Sample	CGW-22-0065-2

#	Time	Area	Height	Width	Area%	Symmetry
1	6.429	2010.6	257.1	0.1212	93.796	0.872
2	7.217	133	15.1	0.1371	6.204	0.904

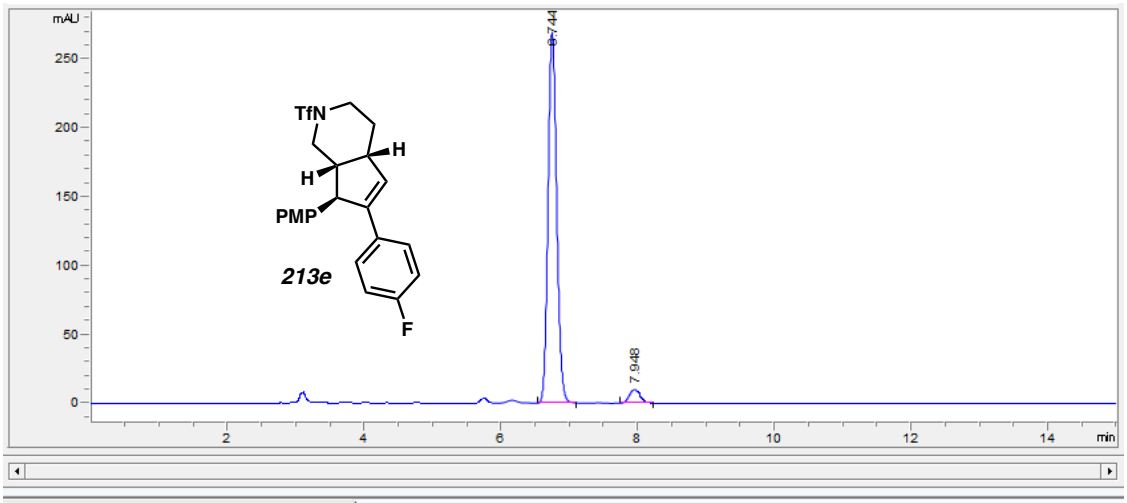


**Recrystallized once from hexanes.*



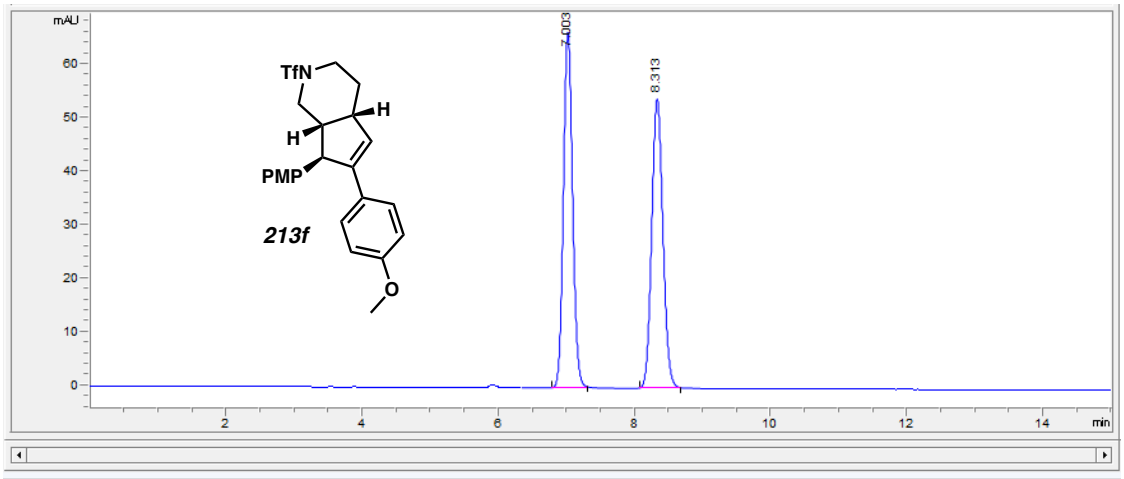
File Information	
LC-File	CGW-22-0070-2-2.D
File Path	C:\Chem32\1\Data\CGW\CGW
Date	04-Mar-22, 08:45:00
Sample	CGW-22-0070-2-2

#	Time	Area	Height	Width	Area%	Symmetry
1	6.779	1379	156.6	0.1367	50.046	0.879
2	7.932	1376.4	128.1	0.1673	49.954	0.862



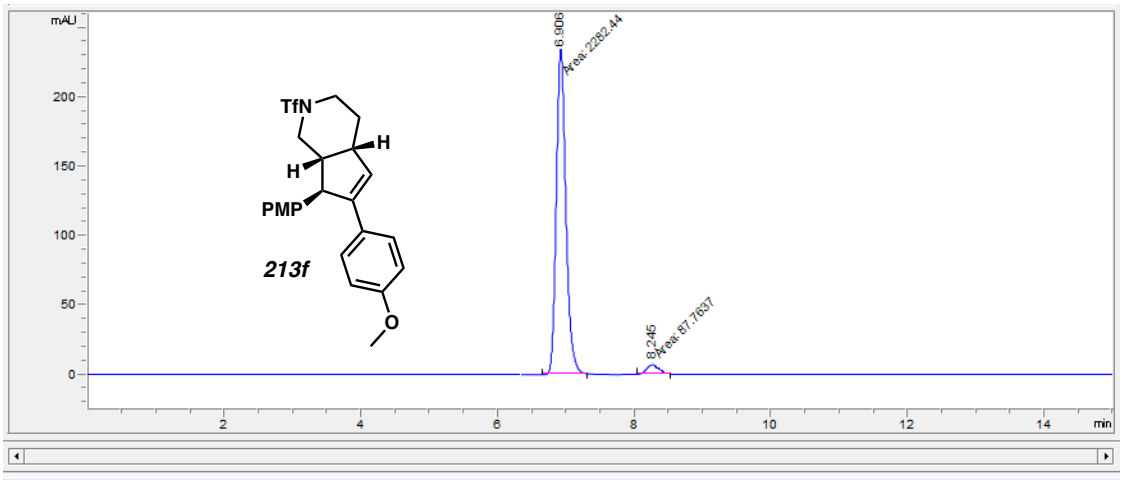
File Information	
LC-File	OnlineEdited--008.D
File Path	C:\Chem32\1\Data\CGW\CGW
Date	13-Mar-22, 12:48:02
Sample	CGW-22-0078-1-again

#	Time	Area	Height	Width	Area%	Symmetry
1	6.744	2384	270.8	0.1367	95.633	0.861
2	7.948	108.9	10.1	0.1689	4.367	0.899



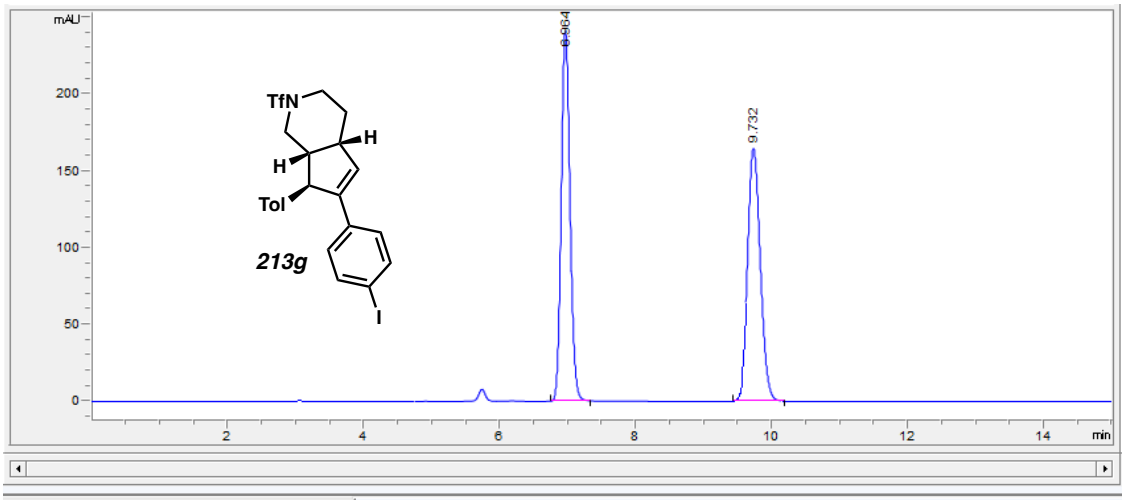
File Information	
LC-File	CGW-22-0067-4redo.D
File Path	C:\Chem32\1\Data\CGW\CGW-2
Date	14-Jun-22, 08:39:19
Sample	CGW-22-0067-4redo

#	Time	Area	Height	Width	Area%	Symmetry
1	7.003	621.5	66.5	0.145	50.137	0.896
2	8.313	618.1	54.1	0.1772	49.863	0.898



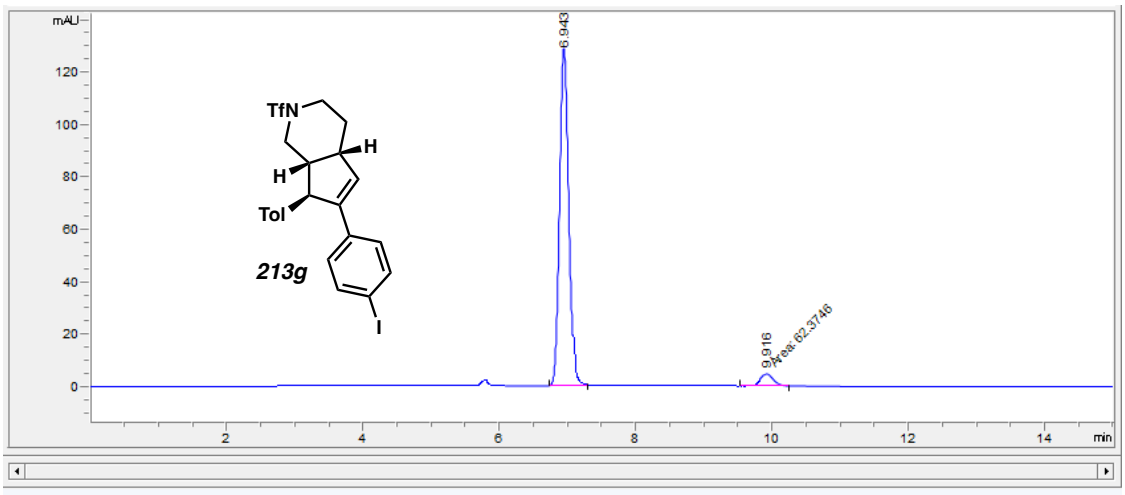
File Information	
LC-File	CGW-22-0067-3again.D
File Path	C:\Chem32\1\Data\CGW\CGW-2
Date	14-Jun-22, 13:14:41
Sample	CGW-22-0067-3again

#	Time	Area	Height	Width	Area%	Symmetry
1	6.906	2282.4	235.3	0.1617	96.297	0.821
2	8.245	87.8	6.9	0.2125	3.703	0.797



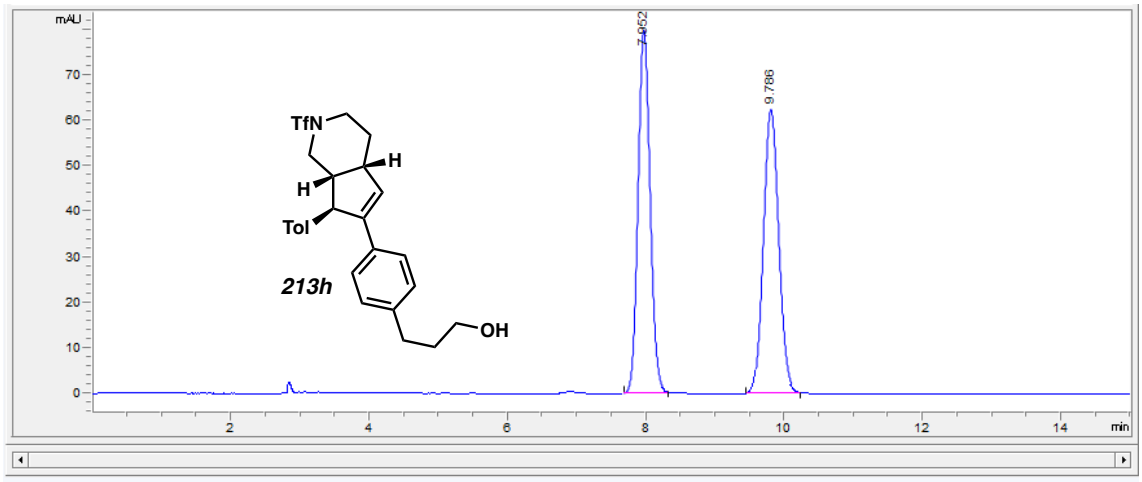
File Information	
LC-File	SKN-22-0037-rac1.D
File Path	C:\Chem32\1\Data\Sepand\SK
Date	10-Feb-22, 17:19:56
Sample	SKN-22-0037-rac1

#	Time	Area	Height	Width	Area%	Symmetry
1	6.964	2167.7	240.8	0.14	49.953	0.854
2	9.732	2171.8	164.3	0.2062	50.047	0.842



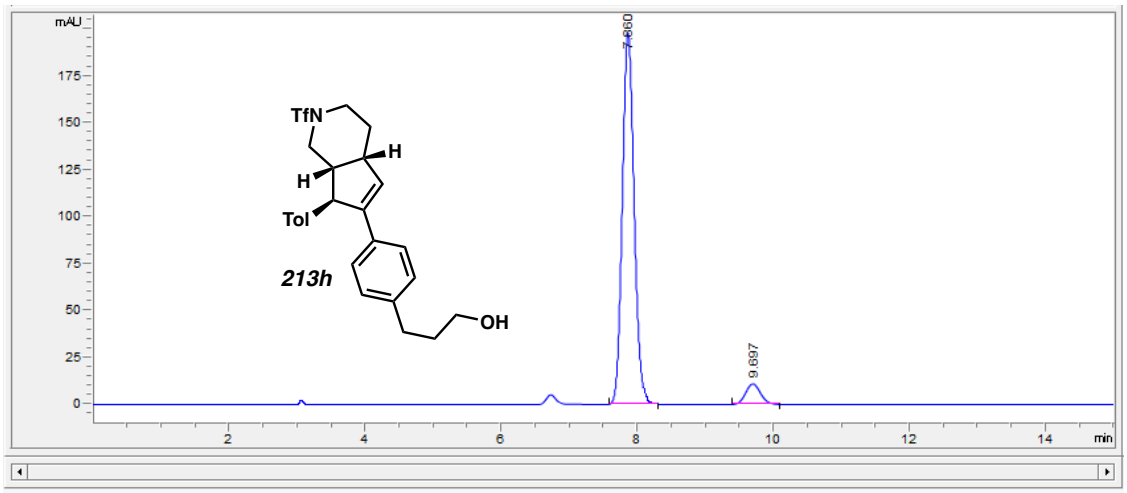
File Information	
LC-File	CGW-22-0095.D
File Path	C:\Chem32\1\Data\CGW\CGW
Date	04-Apr-22, 12:50:58
Sample	CGW-22-0095

#	Time	Area	Height	Width	Area%	Symmetry
1	6.943	1195.4	128.4	0.1456	95.041	0.865
2	9.916	62.4	4.6	0.2272	4.959	0.928



File Information	
LC-File	SKN-22-0104-2.D
File Path	C:\Chem32\1\Data\Sepand\SKN
Date	06-Jun-22, 19:40:07
Sample	SKN-22-0104-2

#	Time	Area	Height	Width	Area%	Symmetry
1	7.952	968.3	79.8	0.1885	50.158	0.891
2	9.786	962.2	62.4	0.24	49.842	0.898



File Information	
LC-File	SKN-22-0104-1.D
File Path	C:\Chem32\1\Data\Sepand\SK
Date	04-May-22, 18:58:44
Sample	SKN-22-0104-1

#	Time	Area	Height	Width	Area%	Symmetry
1	7.86	2380.8	197.6	0.1866	93.393	0.876
2	9.697	168.4	11	0.2379	6.607	0.904

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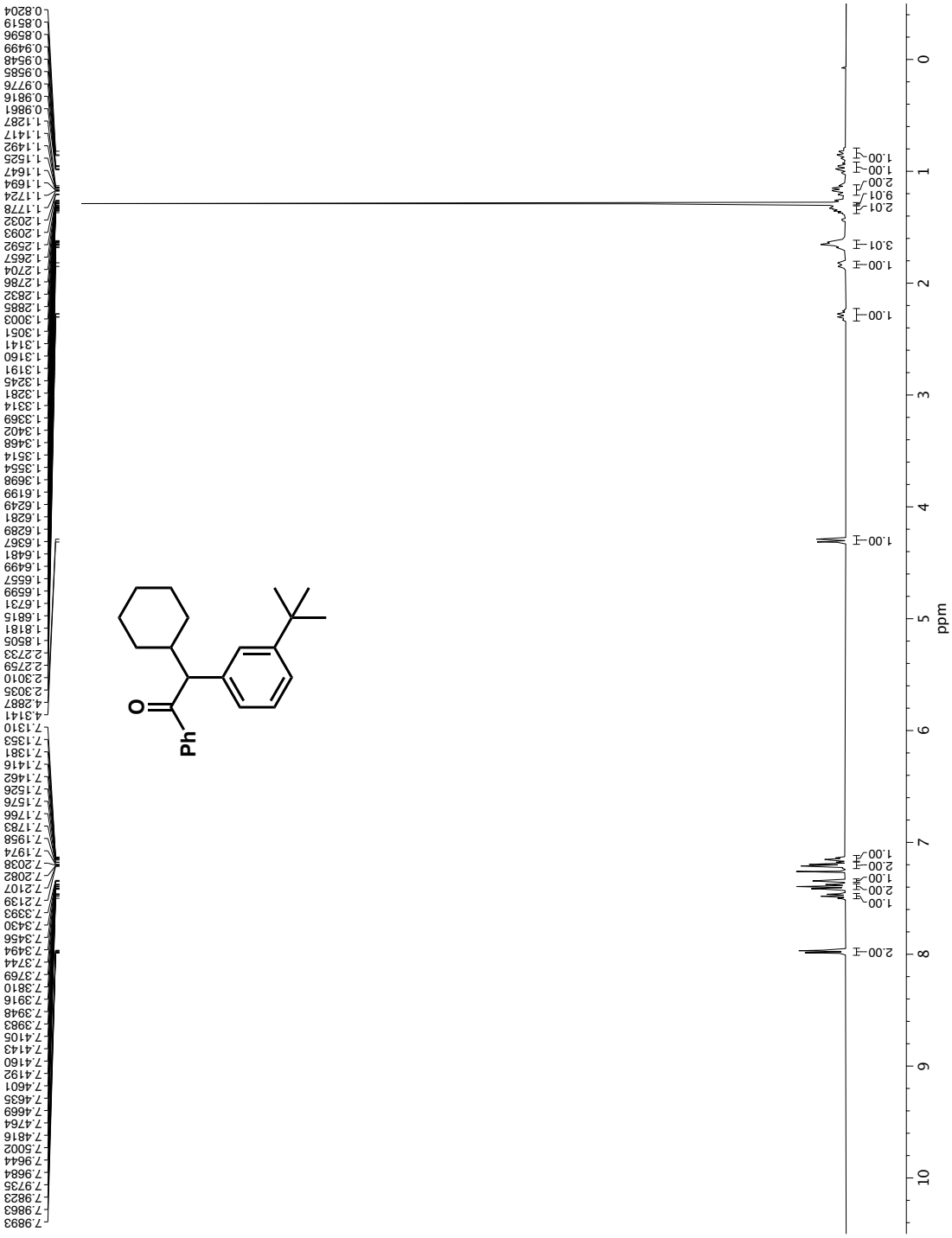
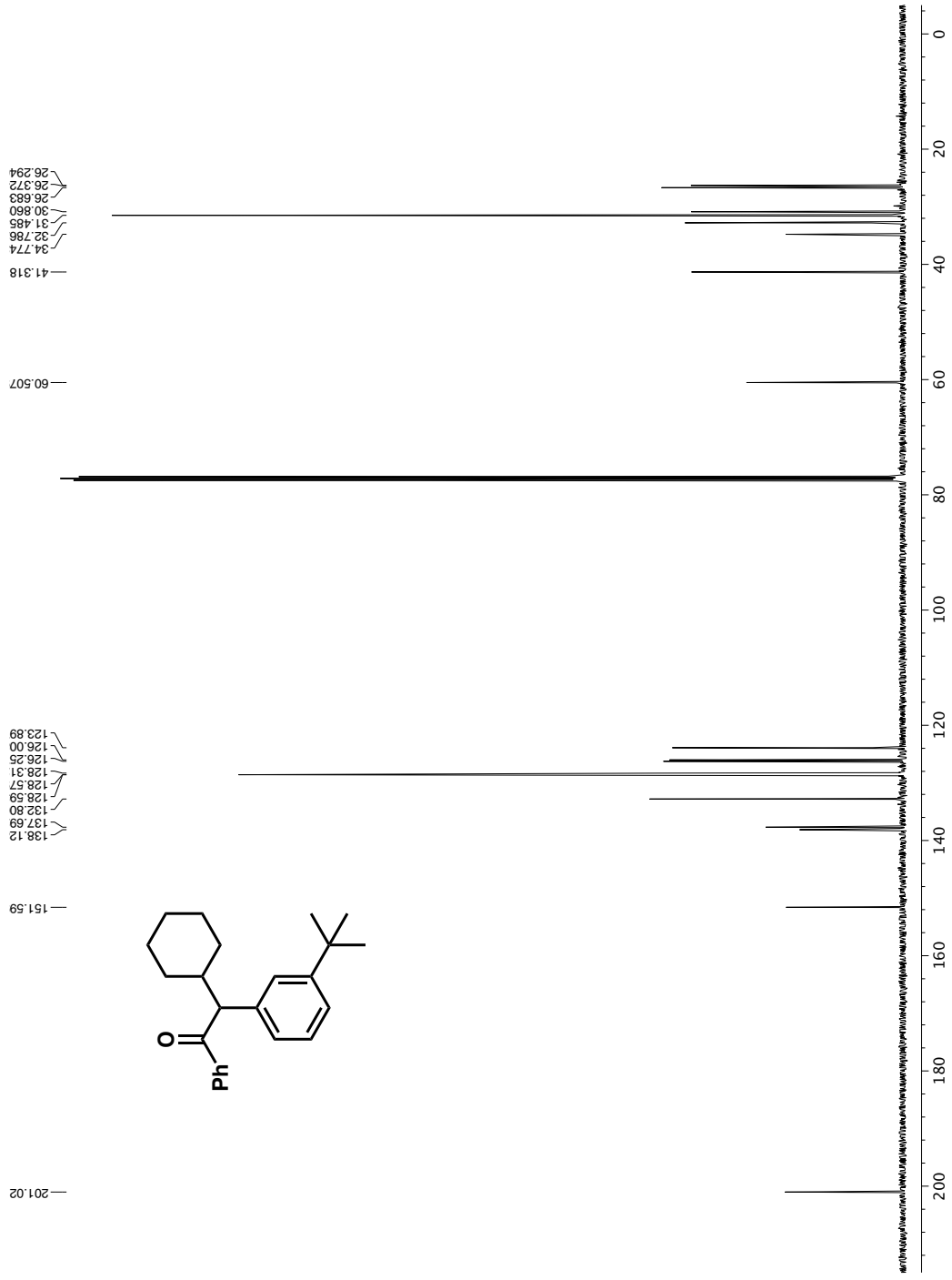
Appendix 3

Spectra Relevant to Chapter 4:

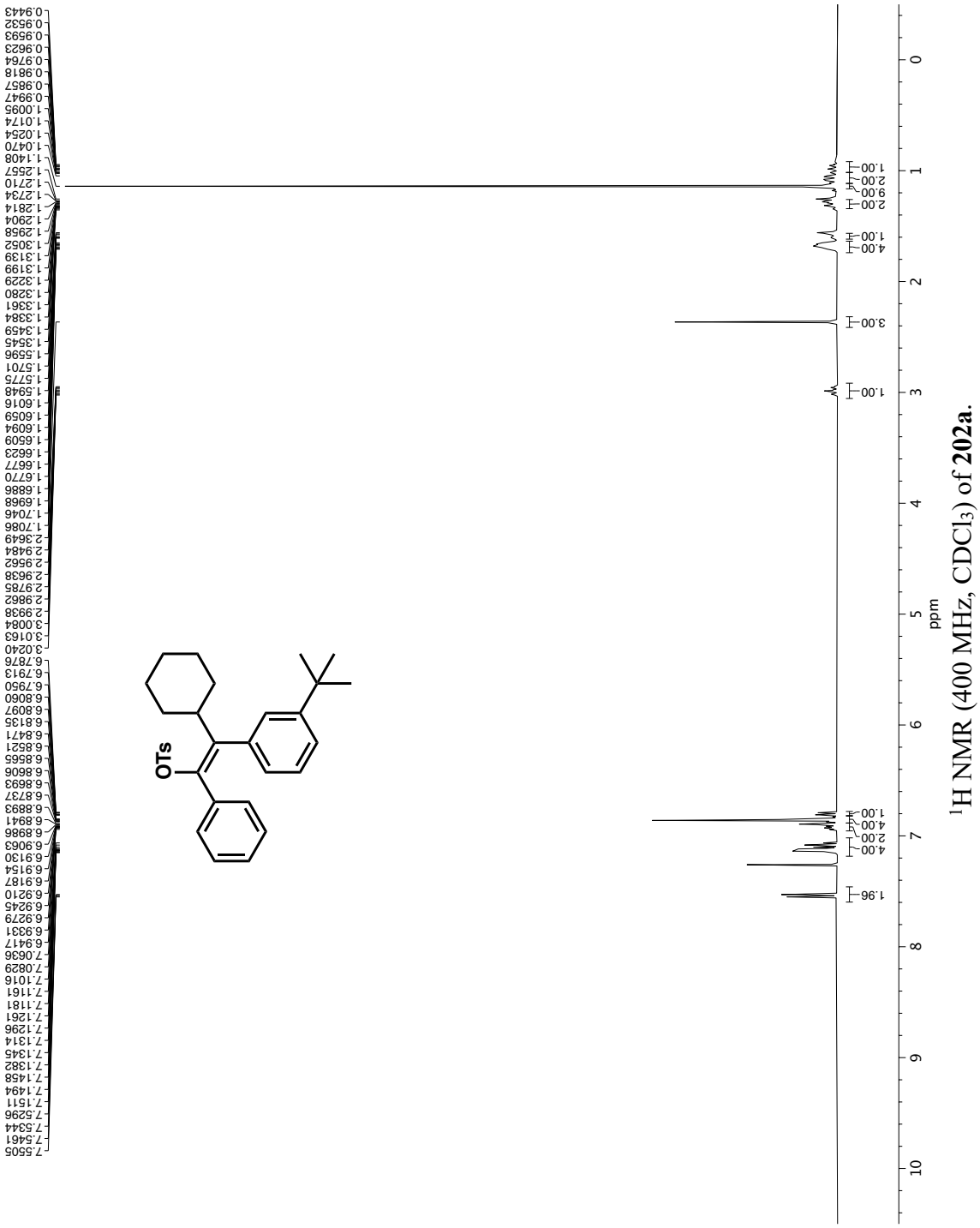
Catalytic Asymmetric C–H Insertion Reactions of Vinyl Carbocations



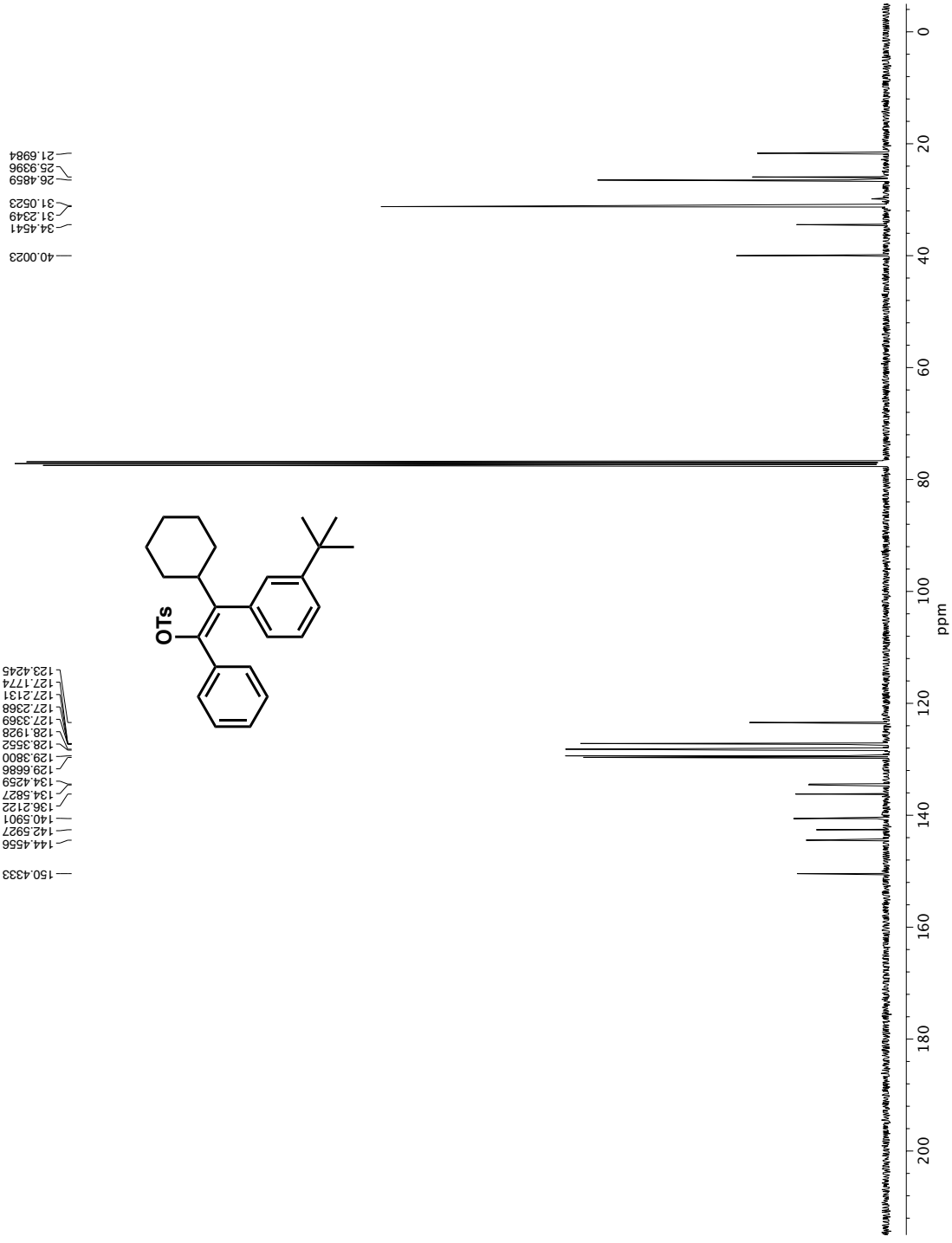
^{1}H NMR (400 MHz, $CDCl_3$) of **215**.



^{13}C NMR (101 MHz, $CDCl_3$) of **215**.



^{1}H NMR (400 MHz, $CDCl_3$) of **202a**.



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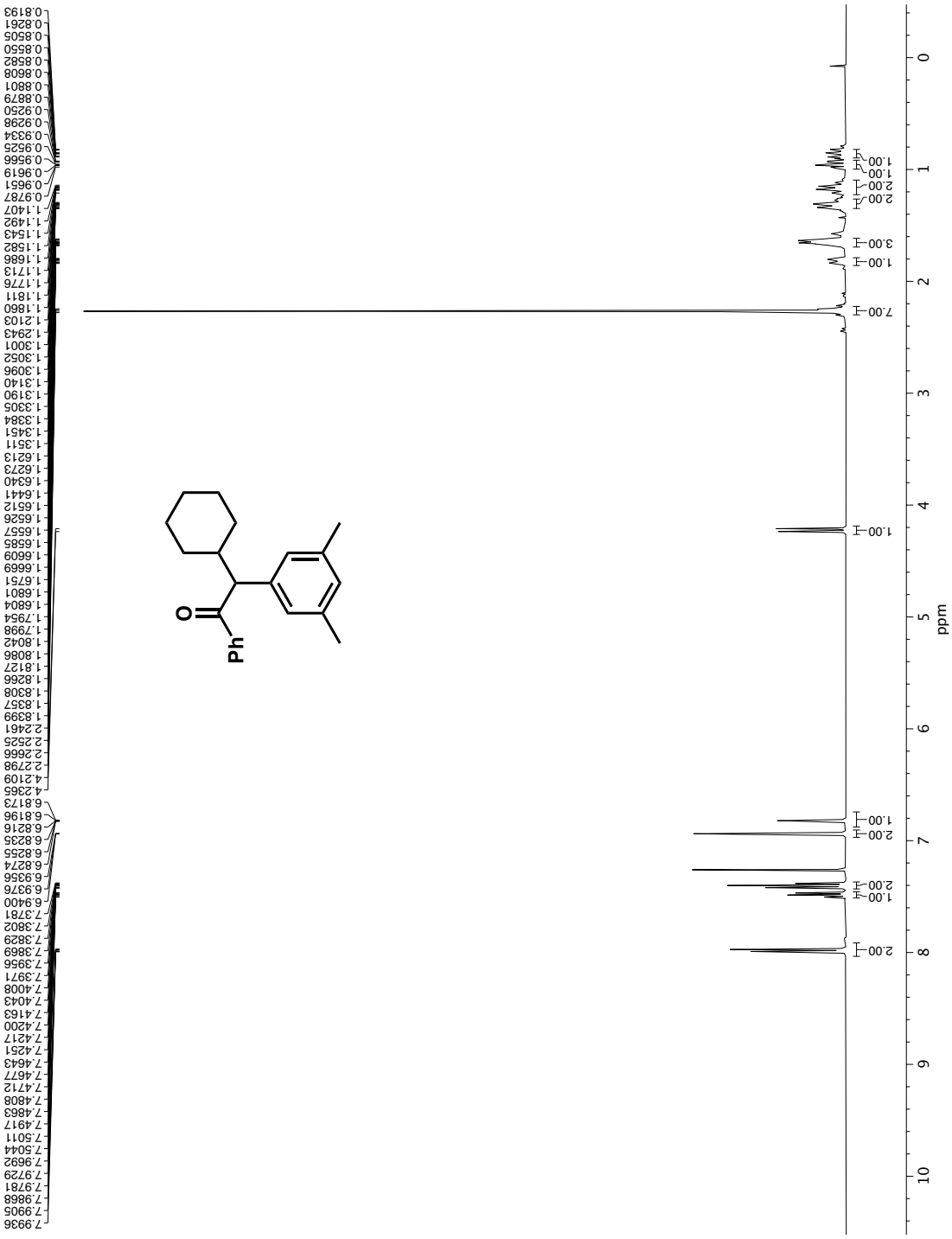
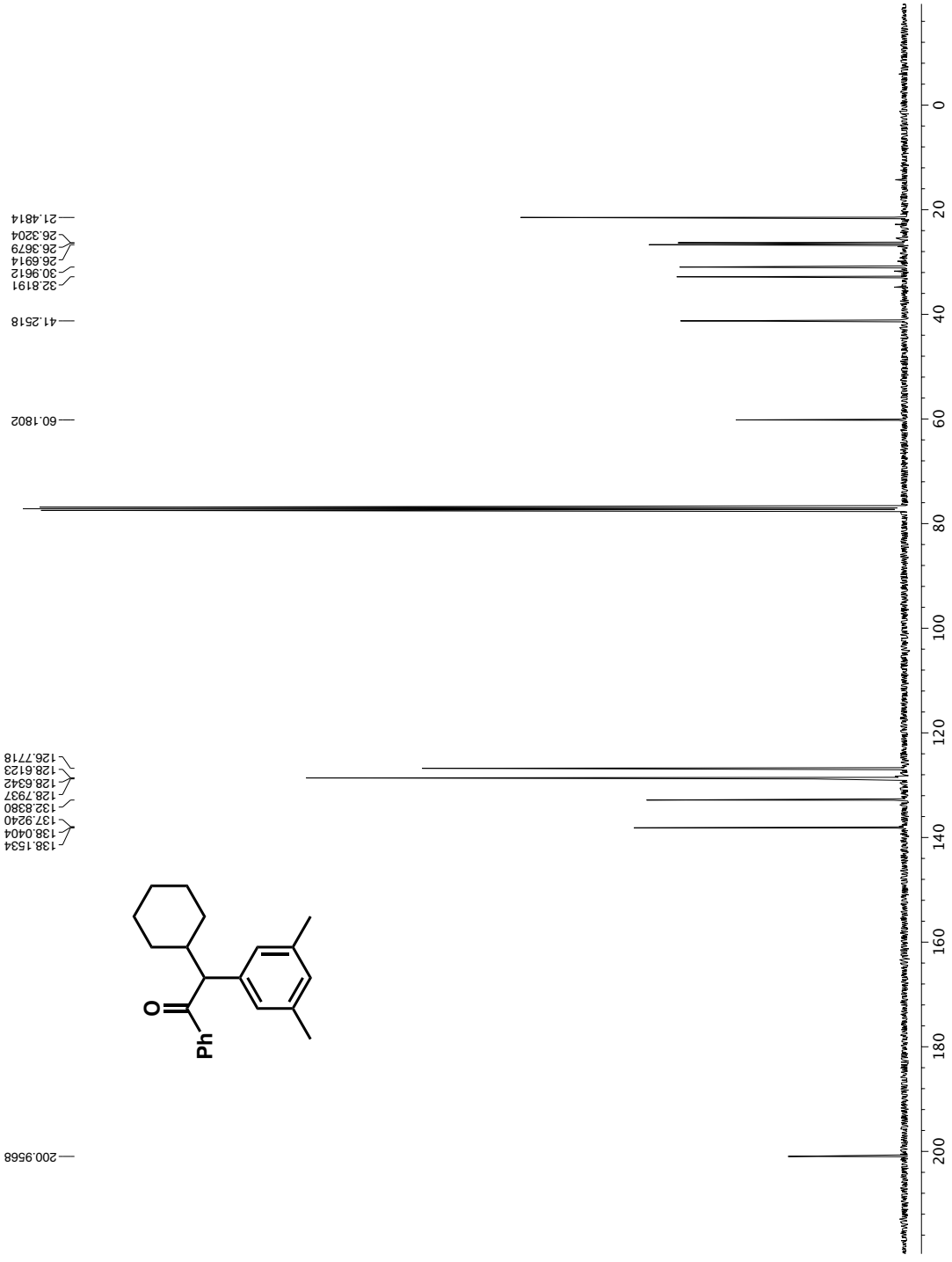


^{1}H NMR (400 MHz, $CDCl_3$) of **216**.



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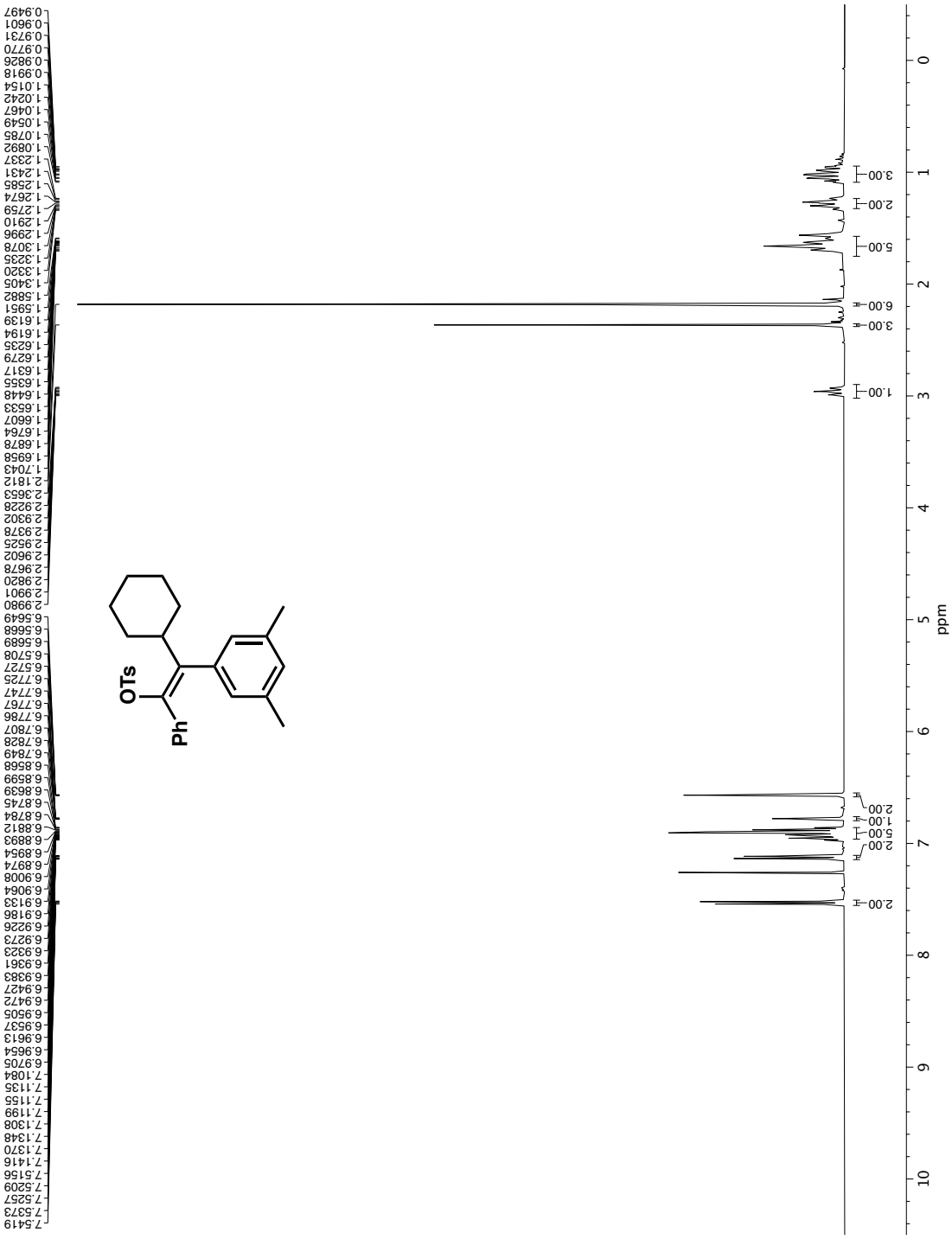
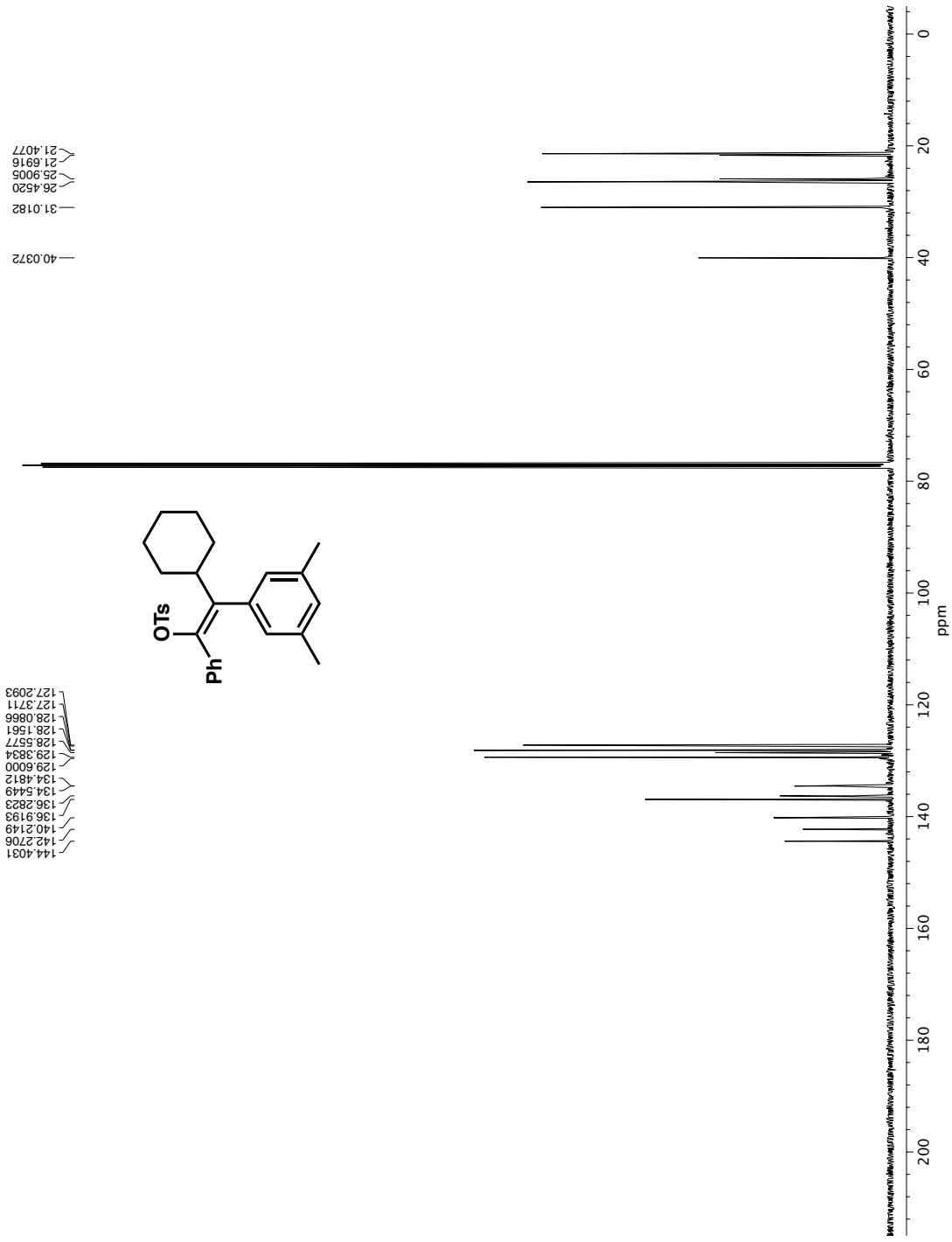
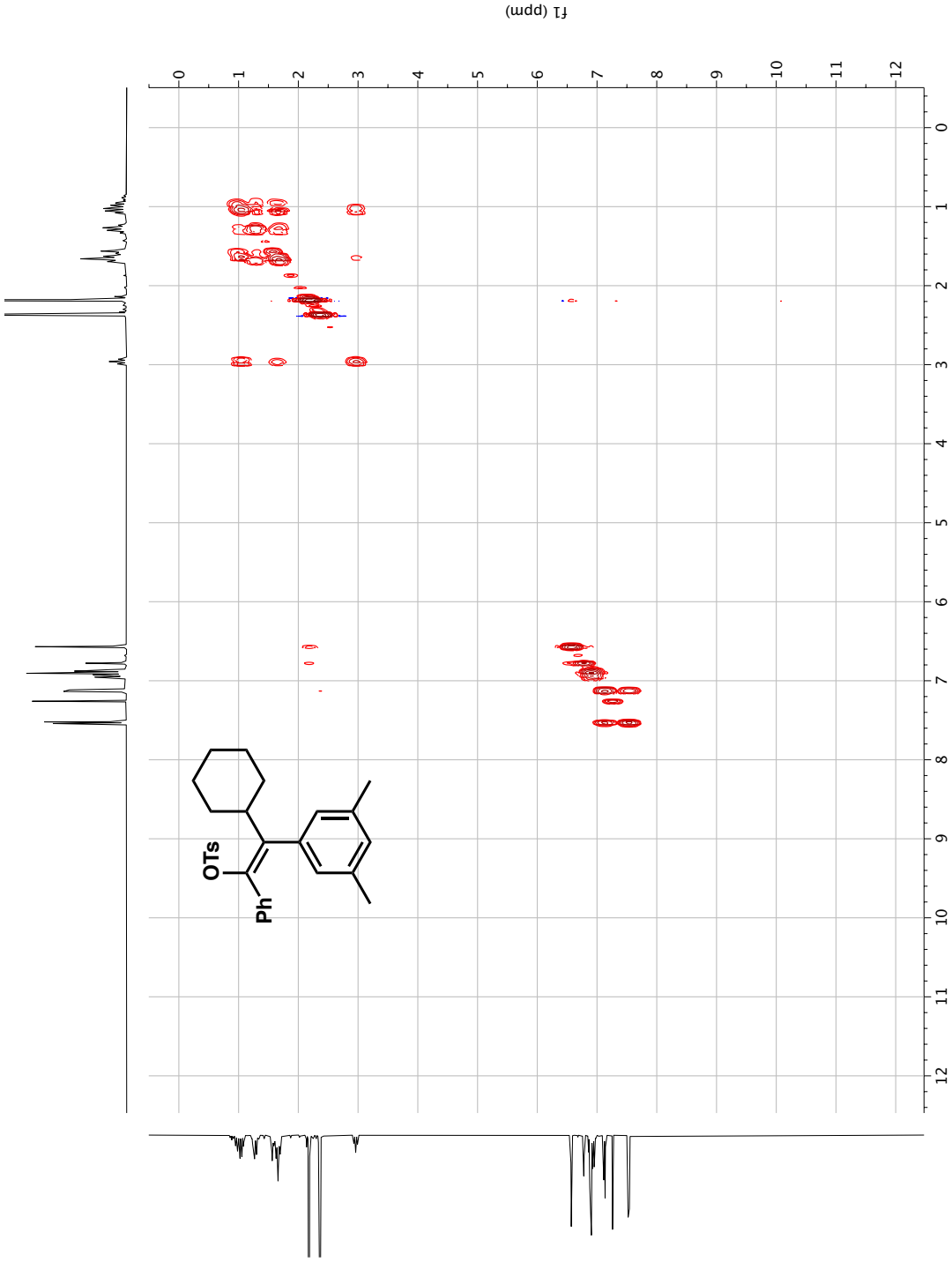


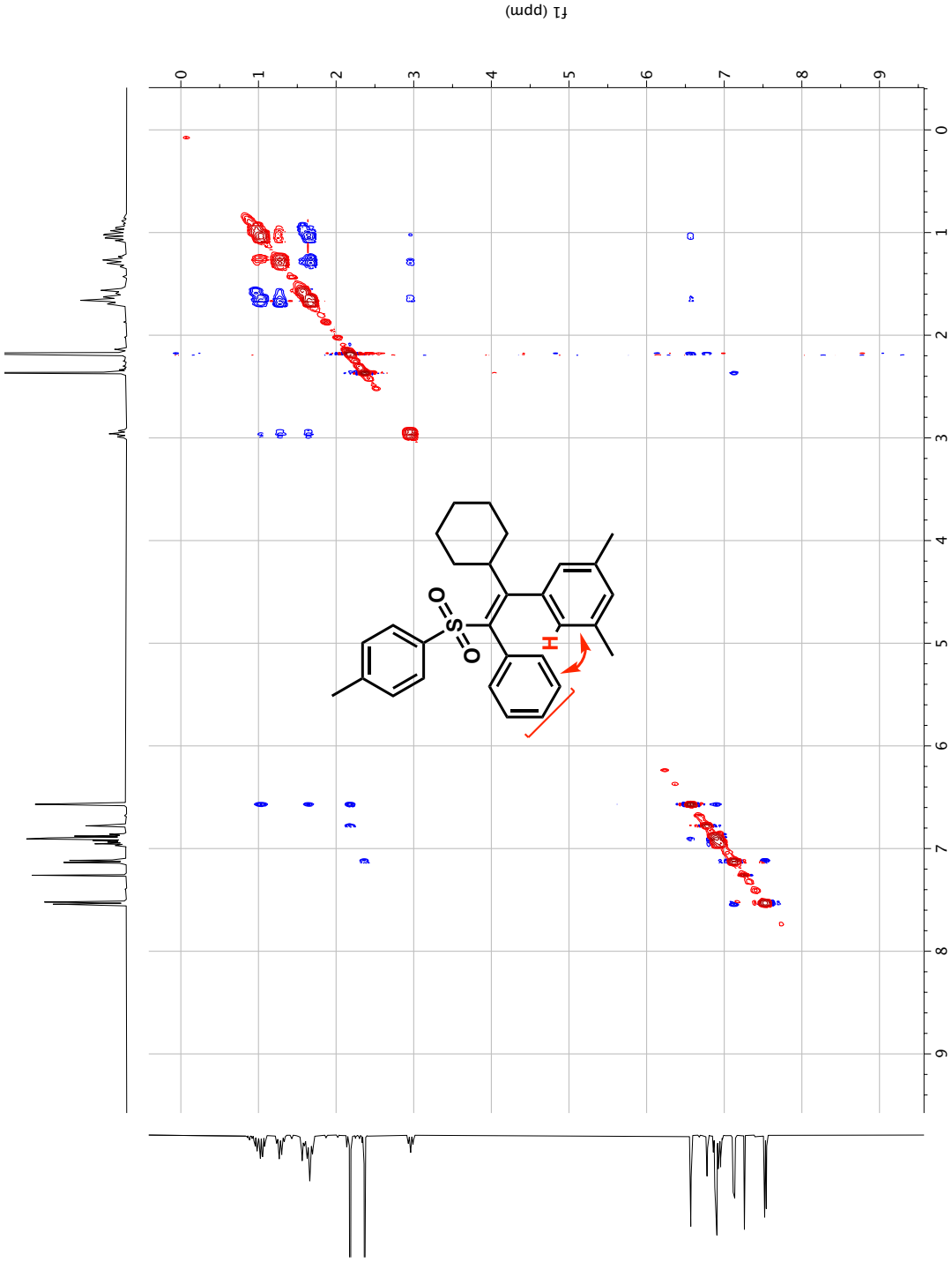
^{1}H NMR (400 MHz, $CDCl_3$) of **202b**.



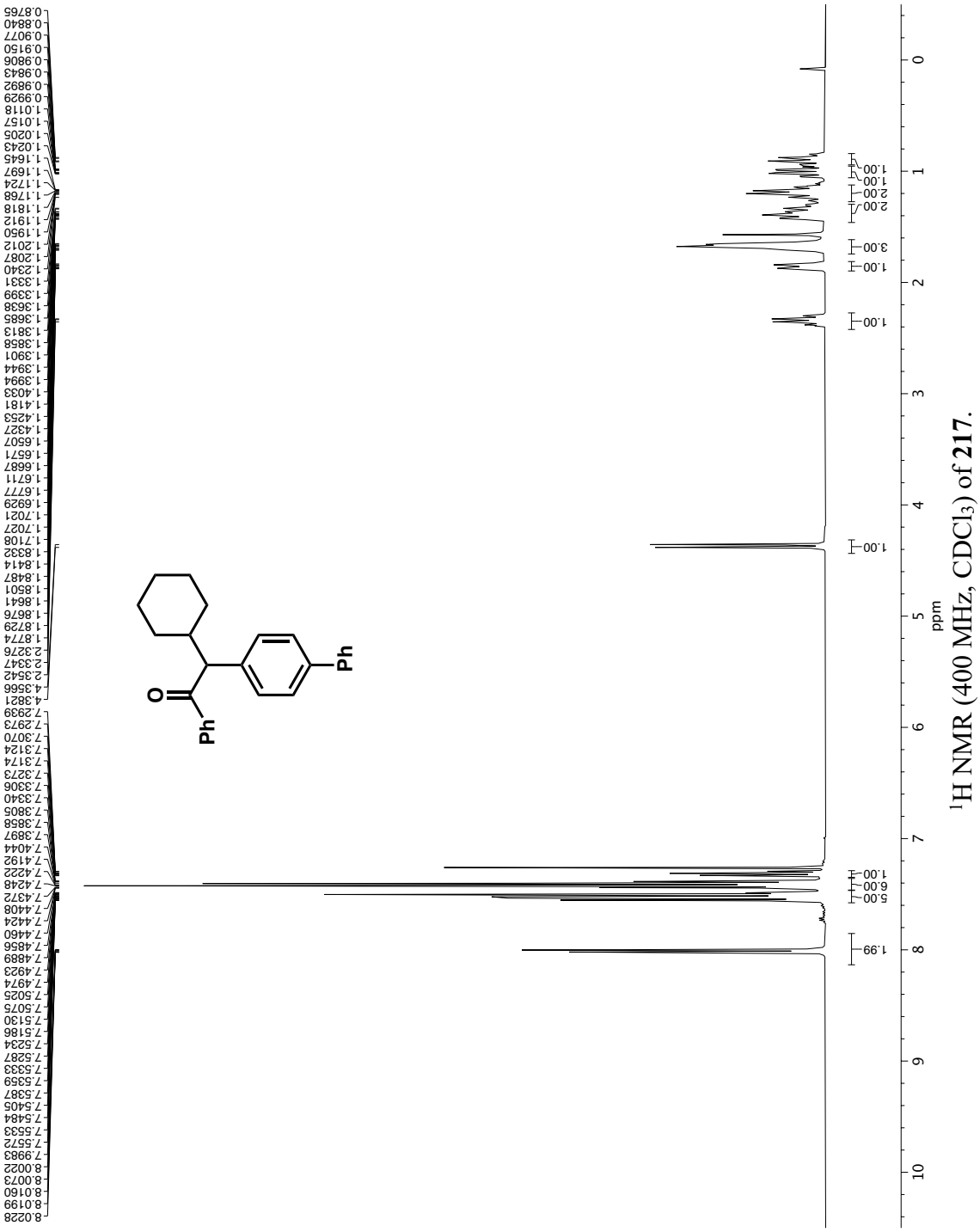
^{13}C NMR (101 MHz, $CDCl_3$) of **202b**.



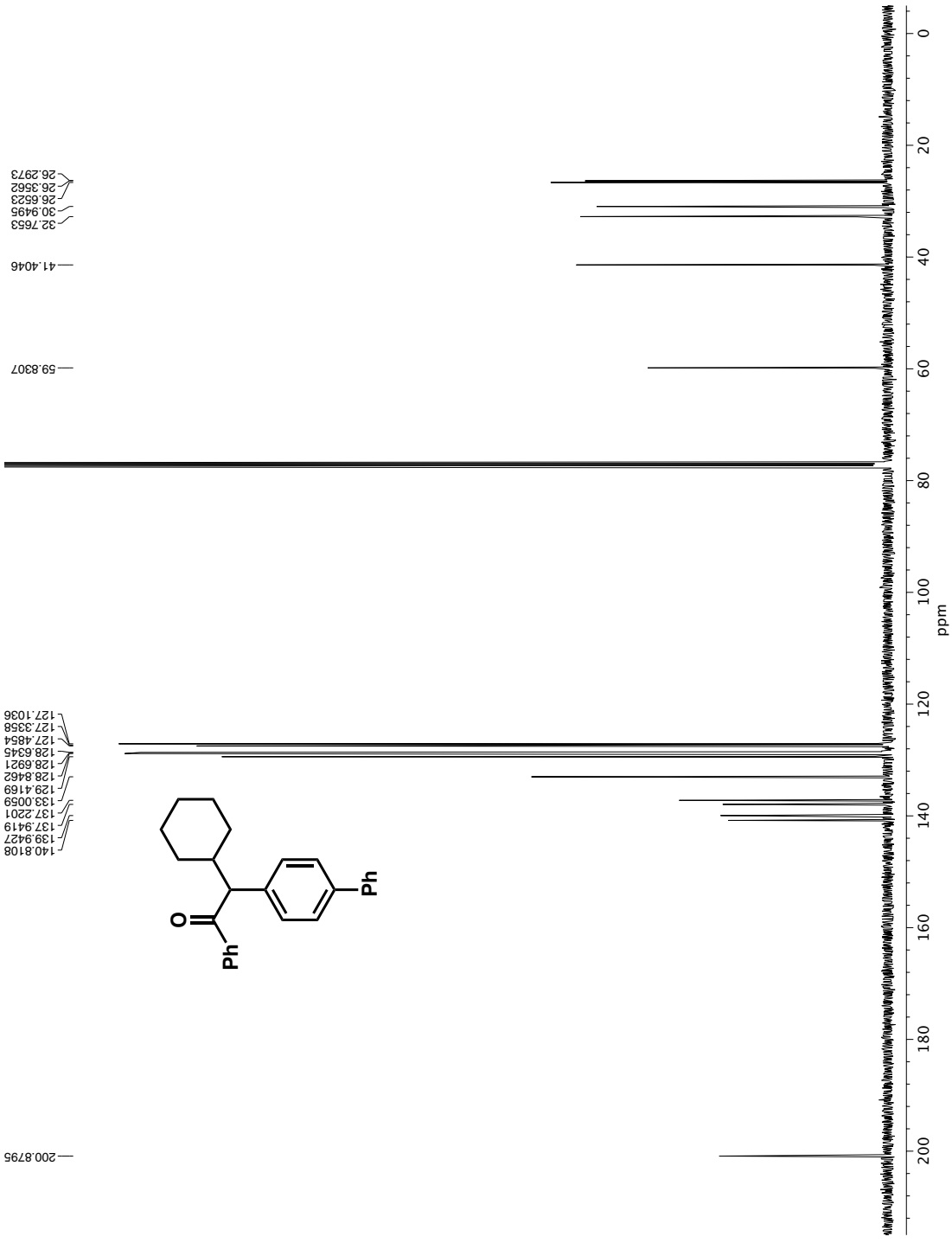
COSY NMR (400 MHz, $CDCl_3$) of **202b**.



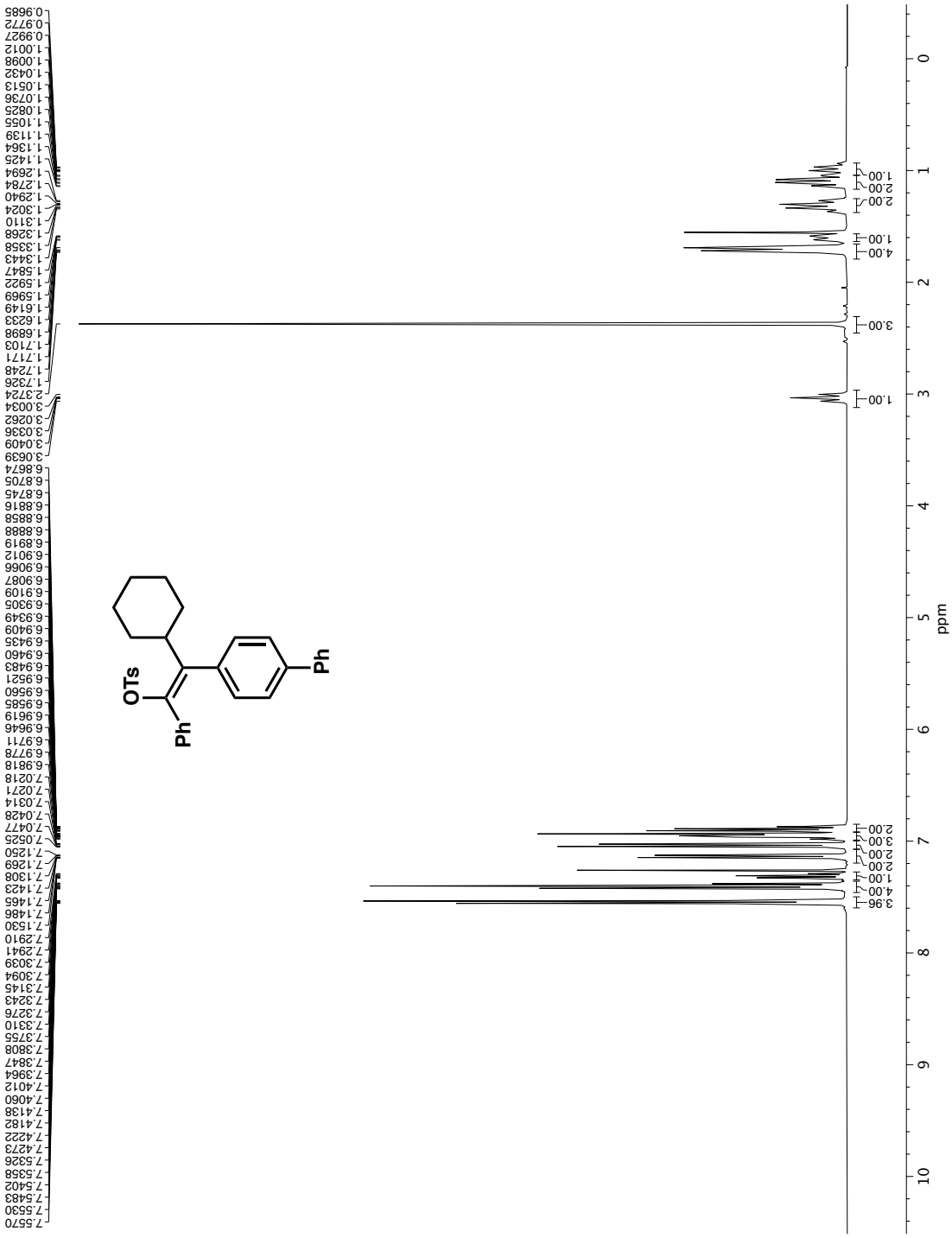
NOESY NMR (400 MHz, $CDCl_3$) of **202b**.



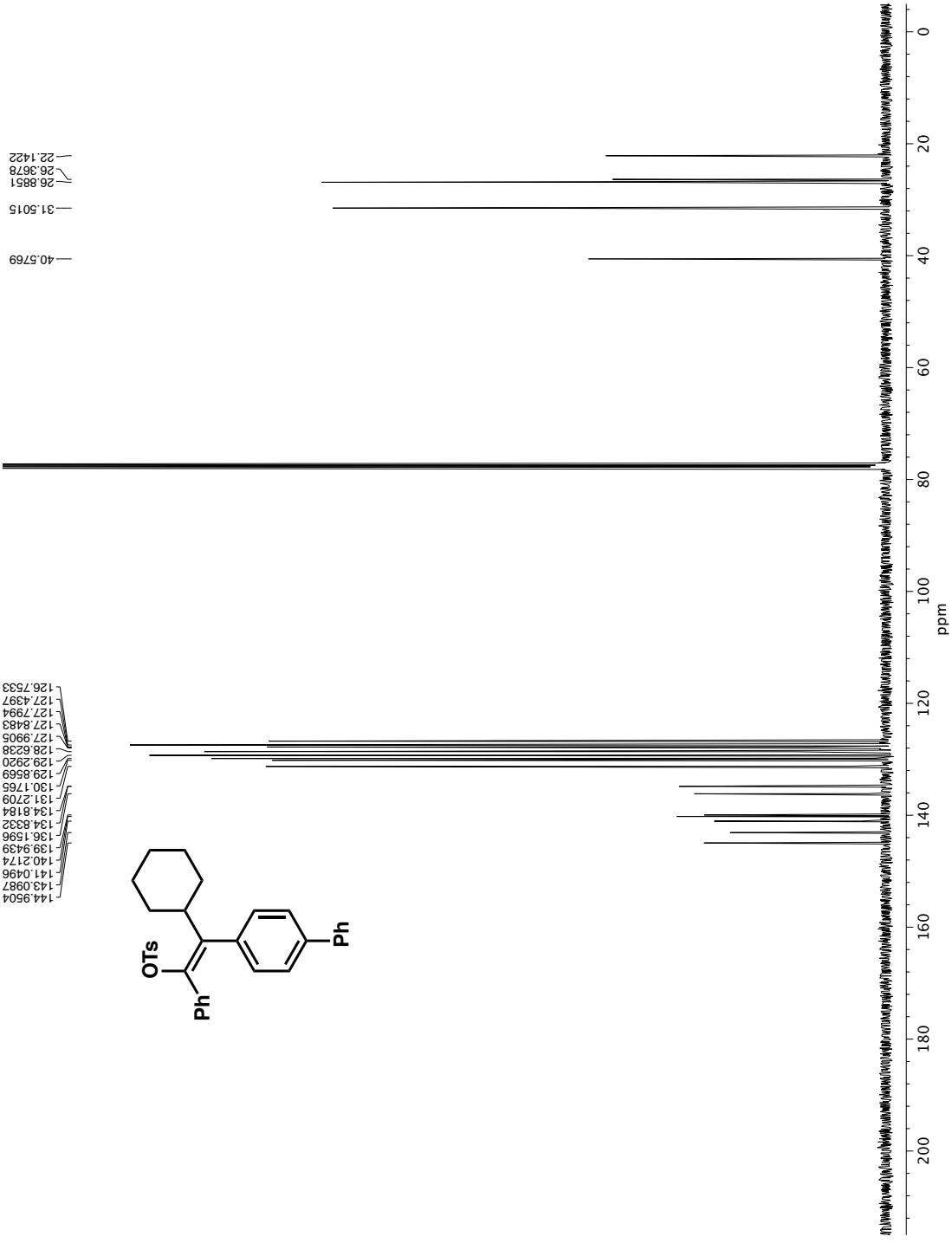
^{1}H NMR (400 MHz, $CDCl_3$) of **217**.



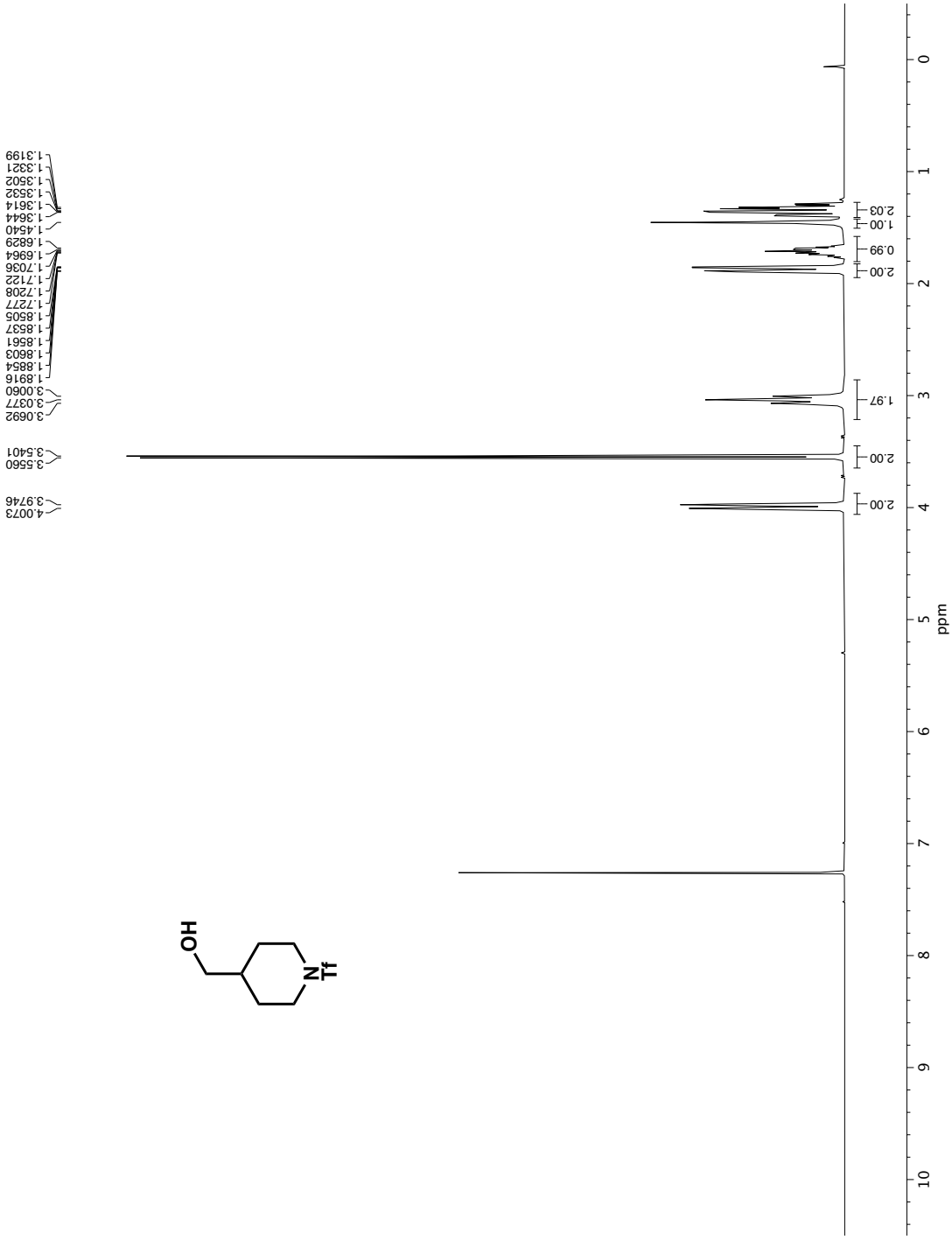
^{13}C NMR (101 MHz, $CDCl_3$) of **217**.



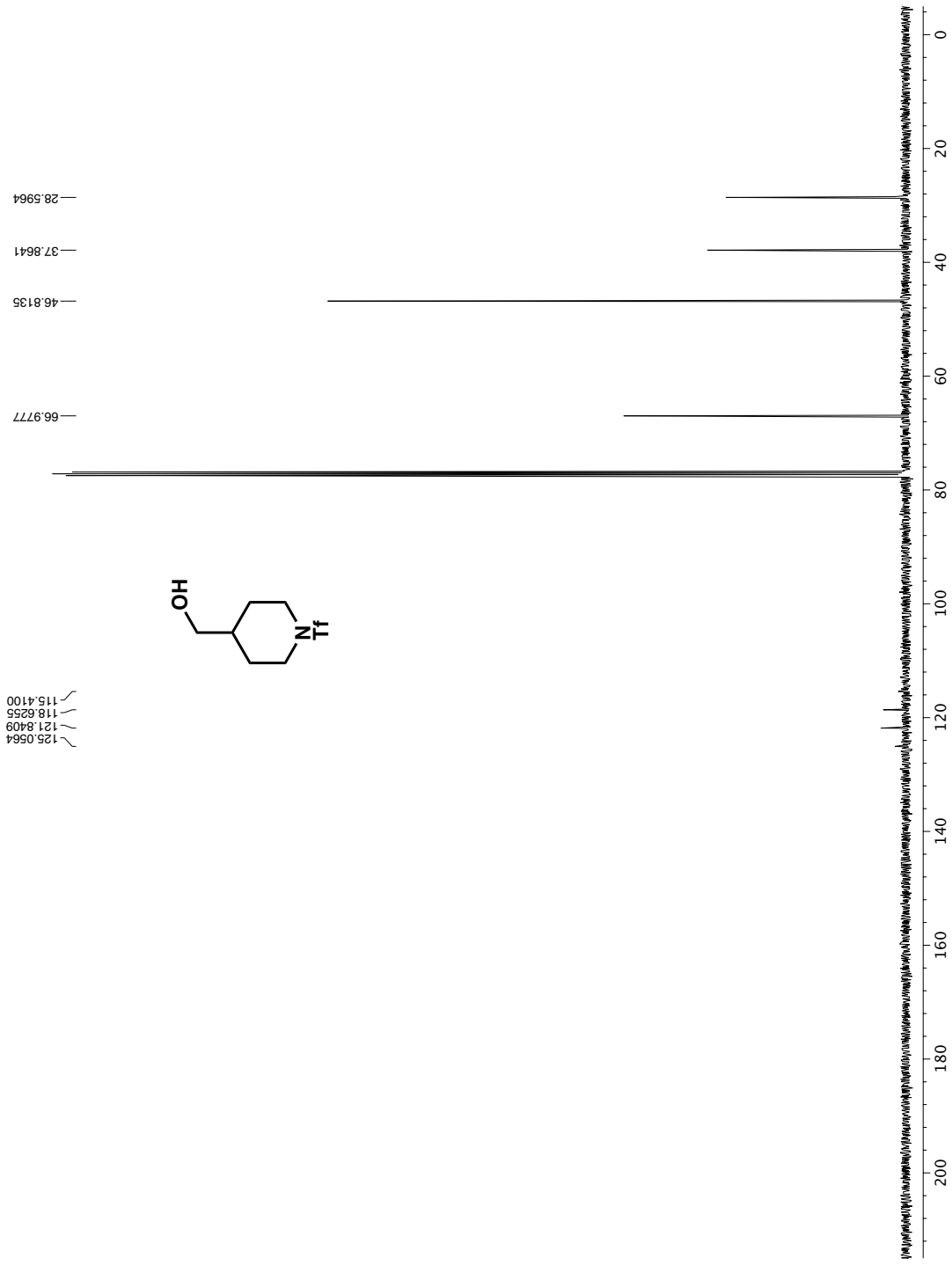
^{1}H NMR (400 MHz, $CDCl_3$) of **202c**.



^{13}C NMR (101 MHz, $CDCl_3$) of **202c**.

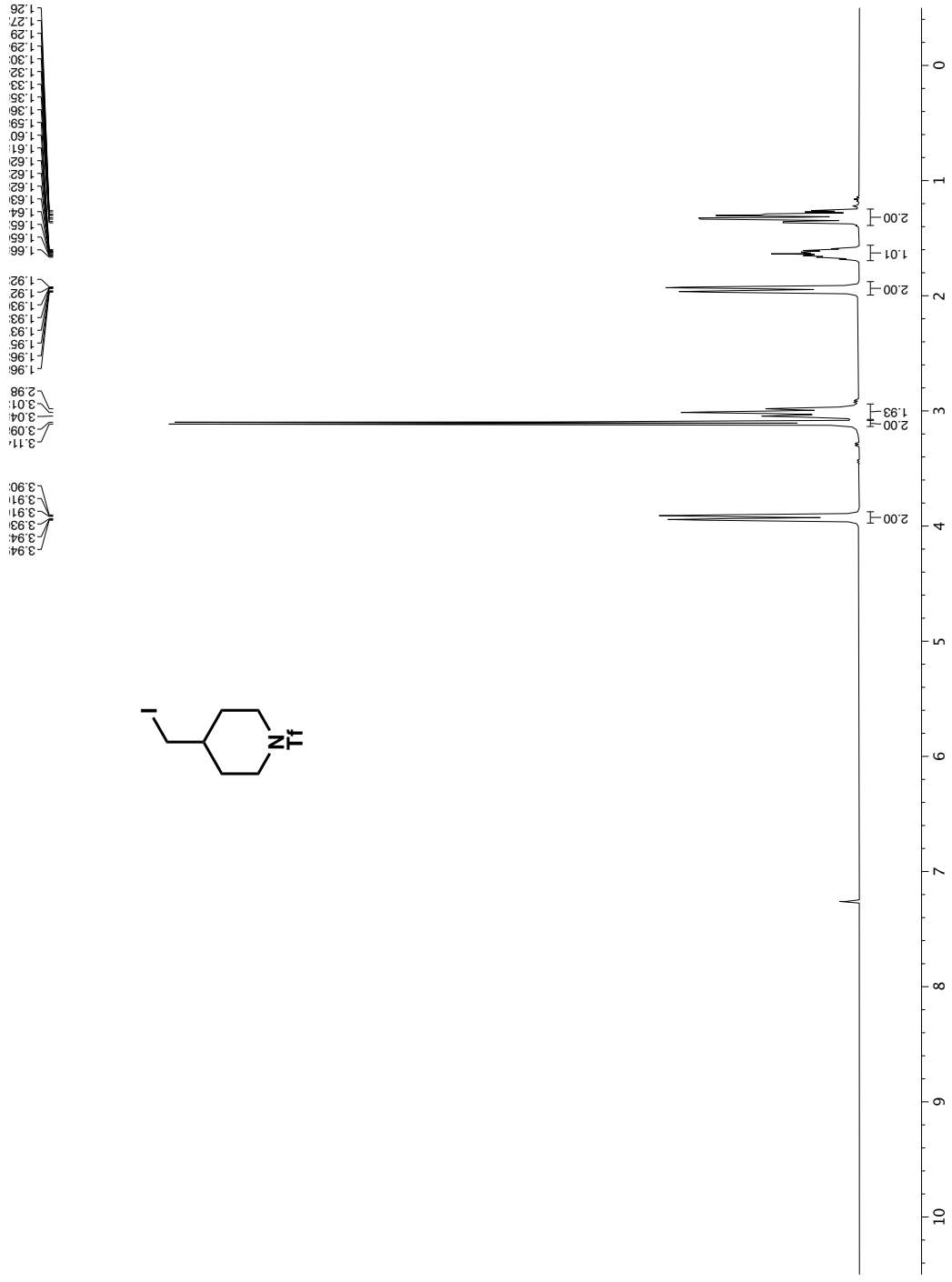


^{1}H NMR (400 MHz, $CDCl_3$) of **218**.



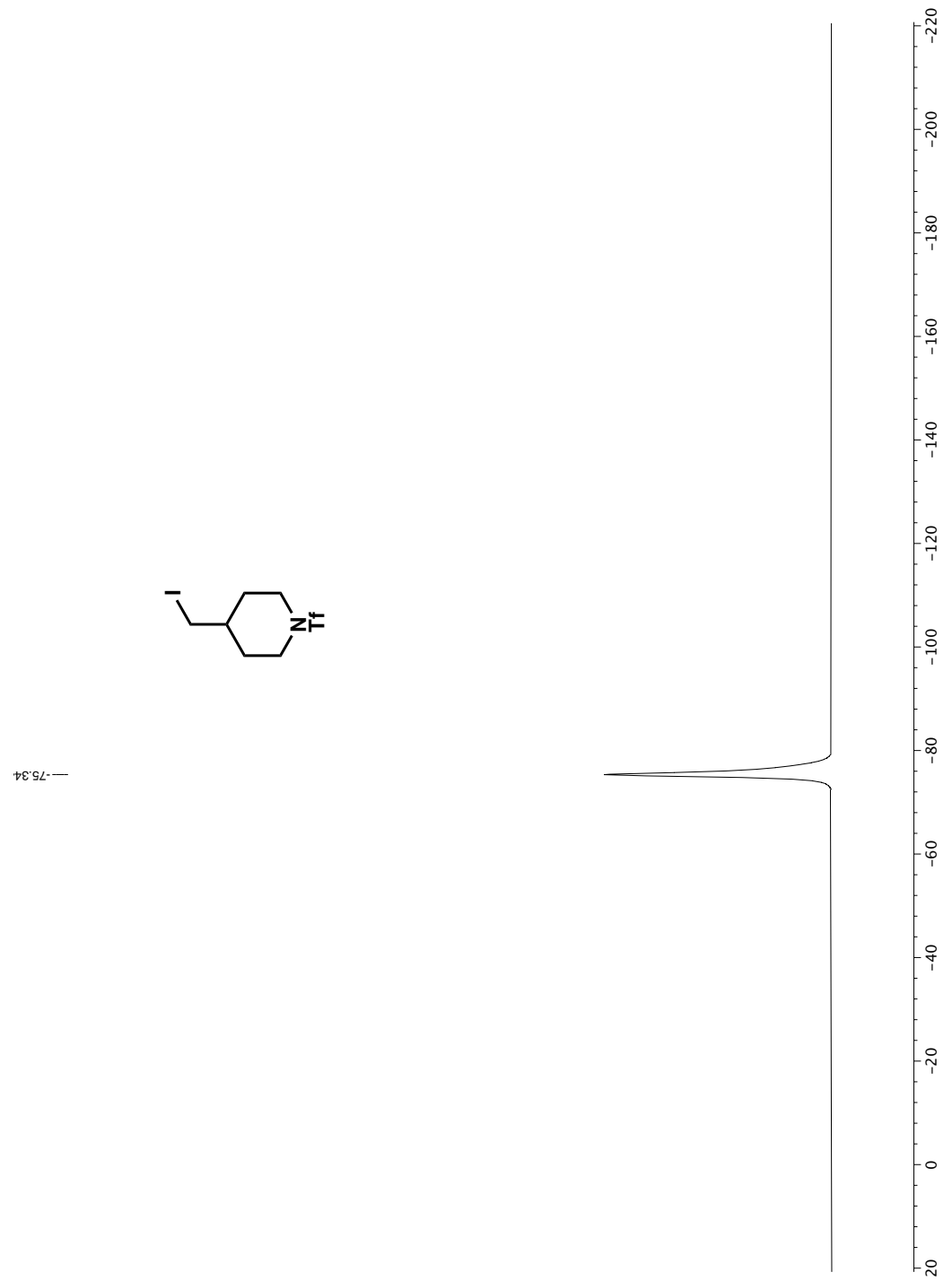
^{13}C NMR (101 MHz, $CDCl_3$) of **218**.

^{19}F NMR (376 MHz, $CDCl_3$) of **218**.

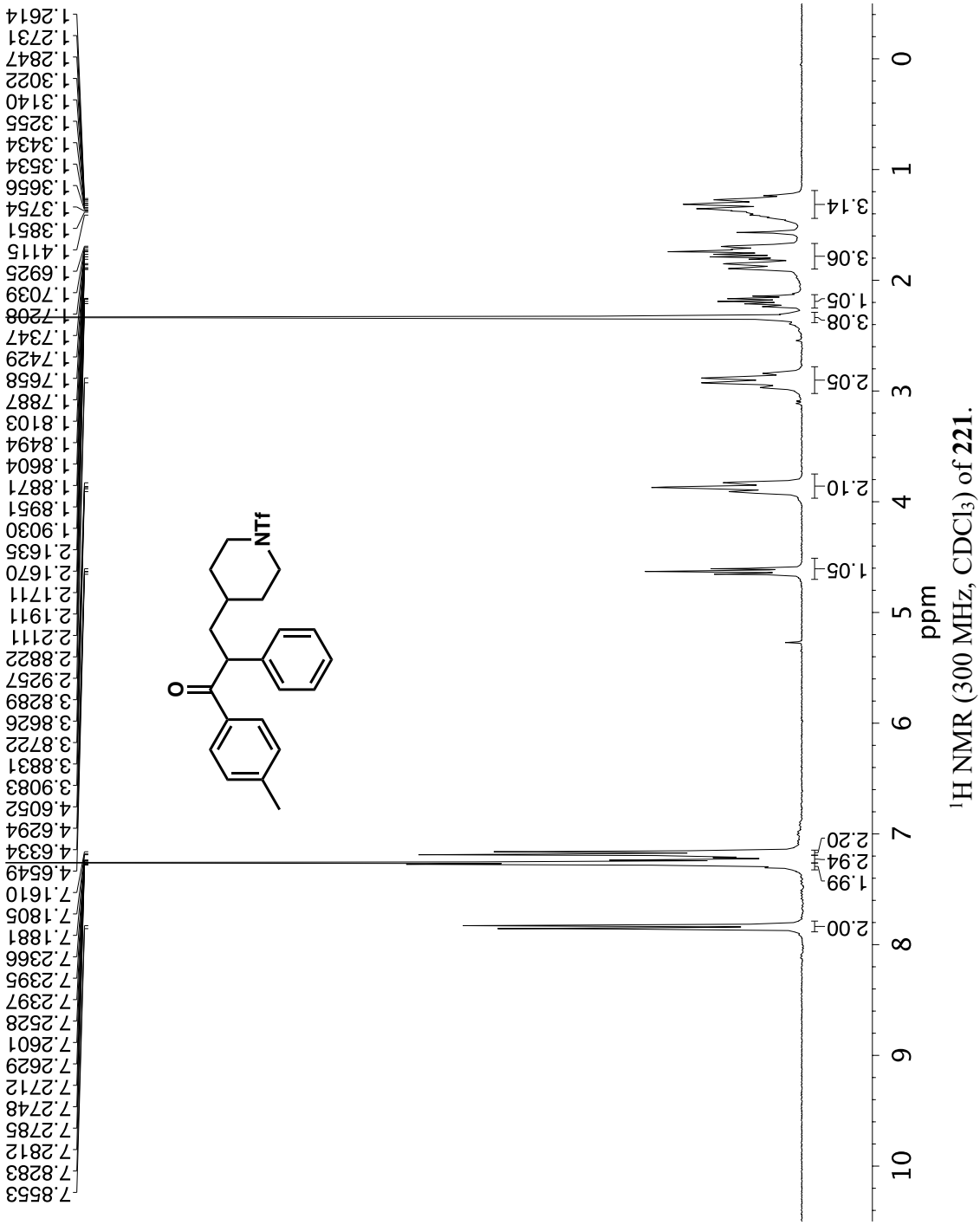


^{1}H NMR (400 MHz, $CDCl_3$) of **219**.

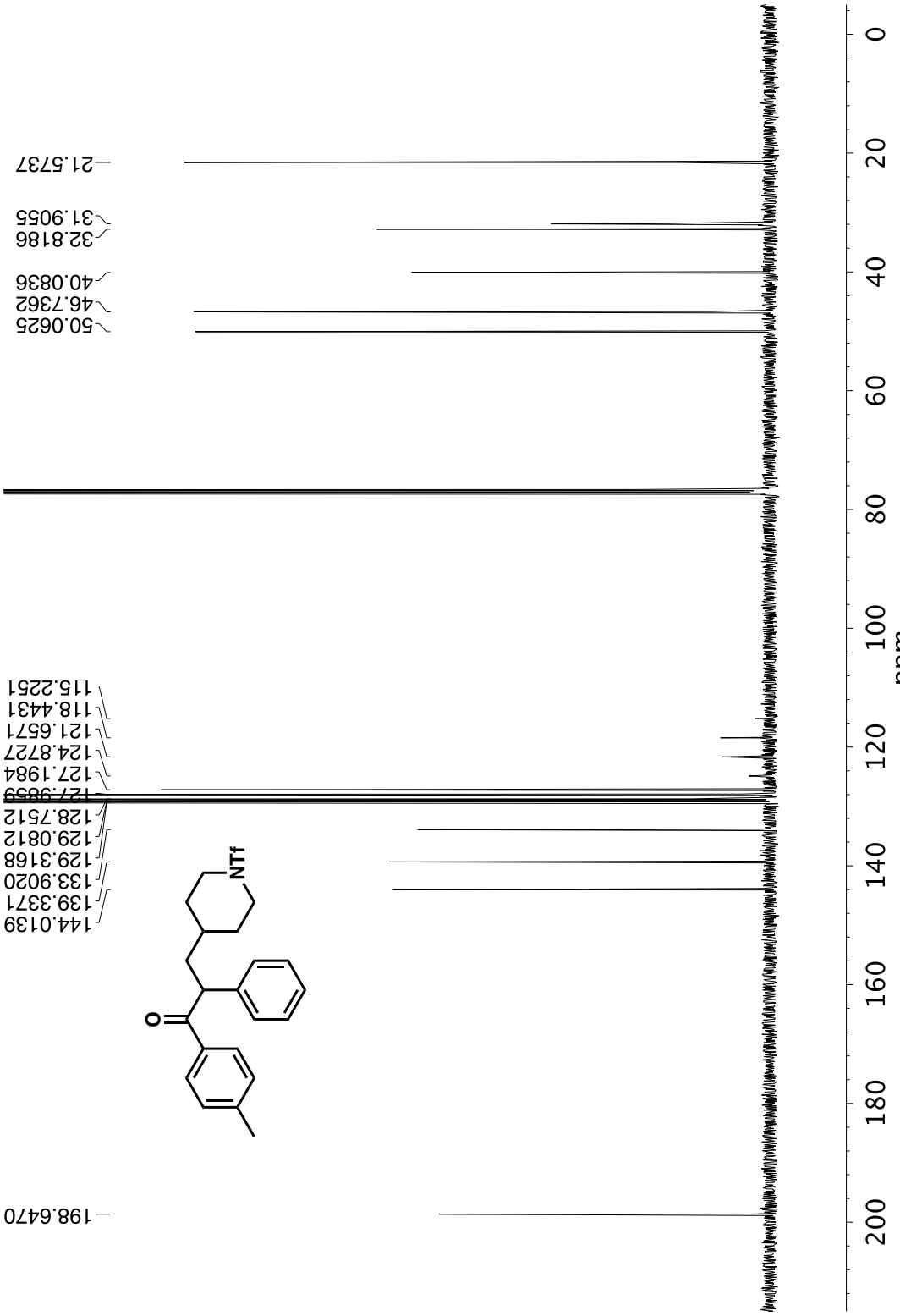
^{13}C NMR (101 MHz, $CDCl_3$) of **219**.



^{19}F NMR (376 MHz, $CDCl_3$) of **219**.

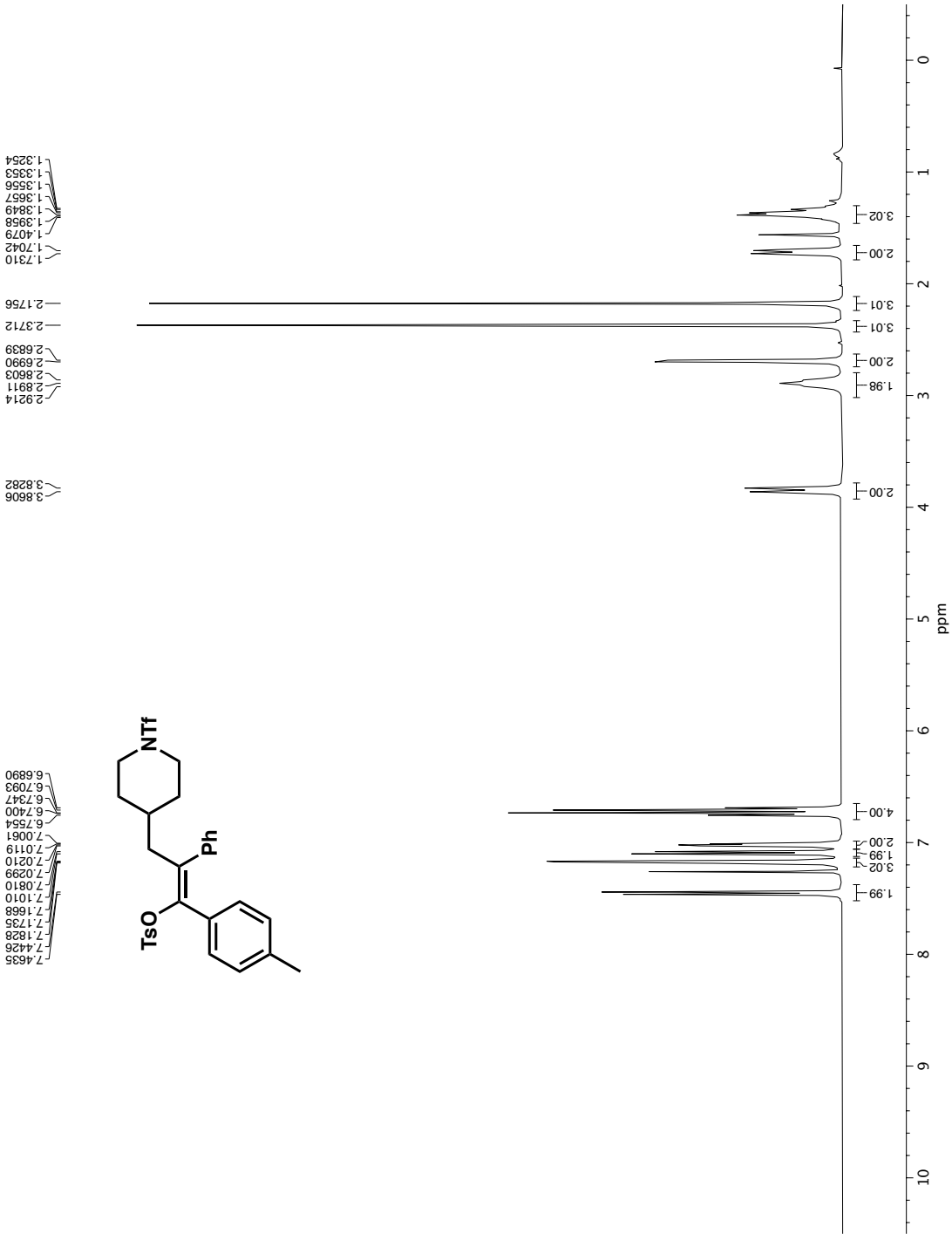


^{1}H NMR (300 MHz, $CDCl_3$) of **221**.

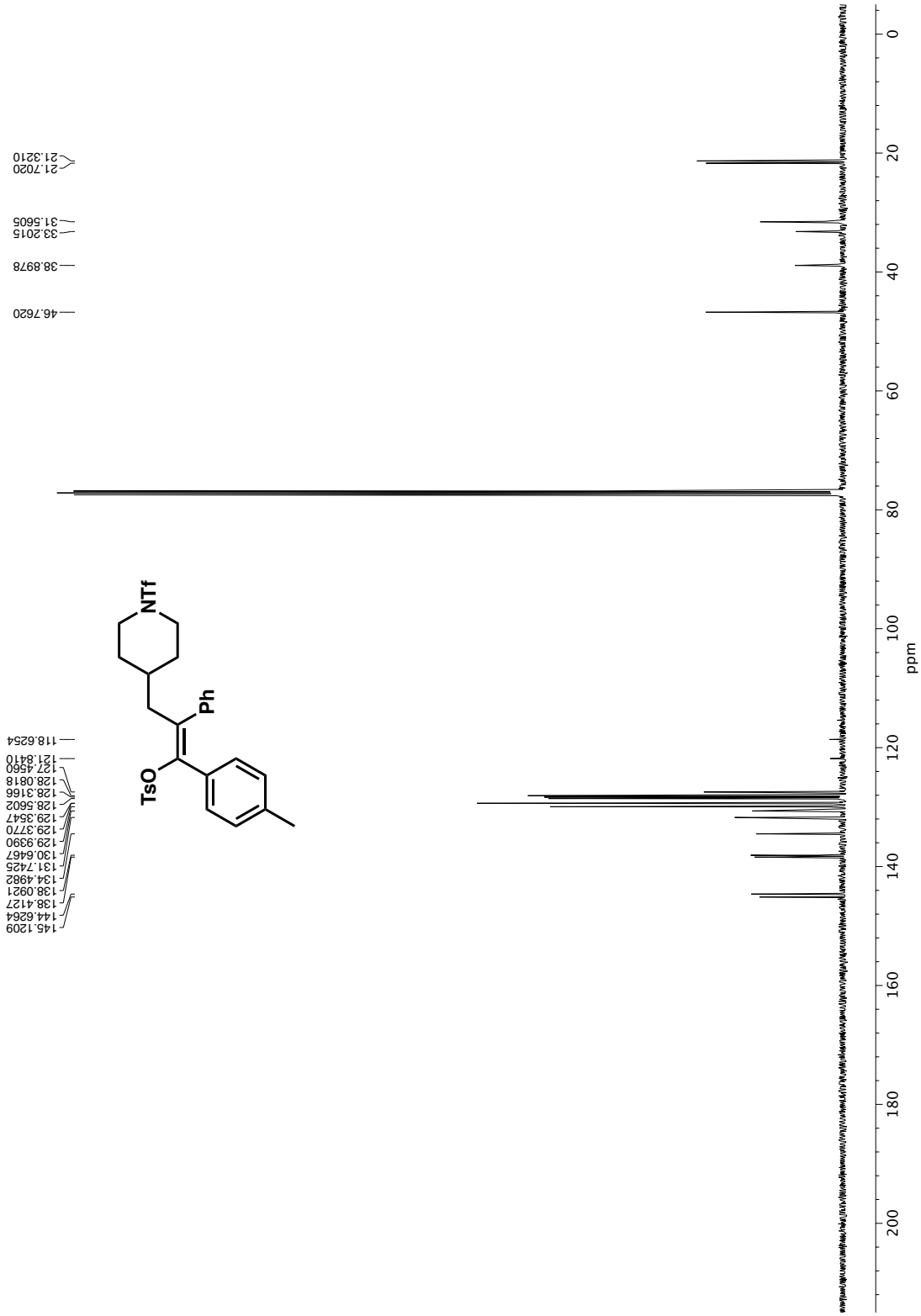


^{13}C NMR (101 MHz, $CDCl_3$) of **221**.

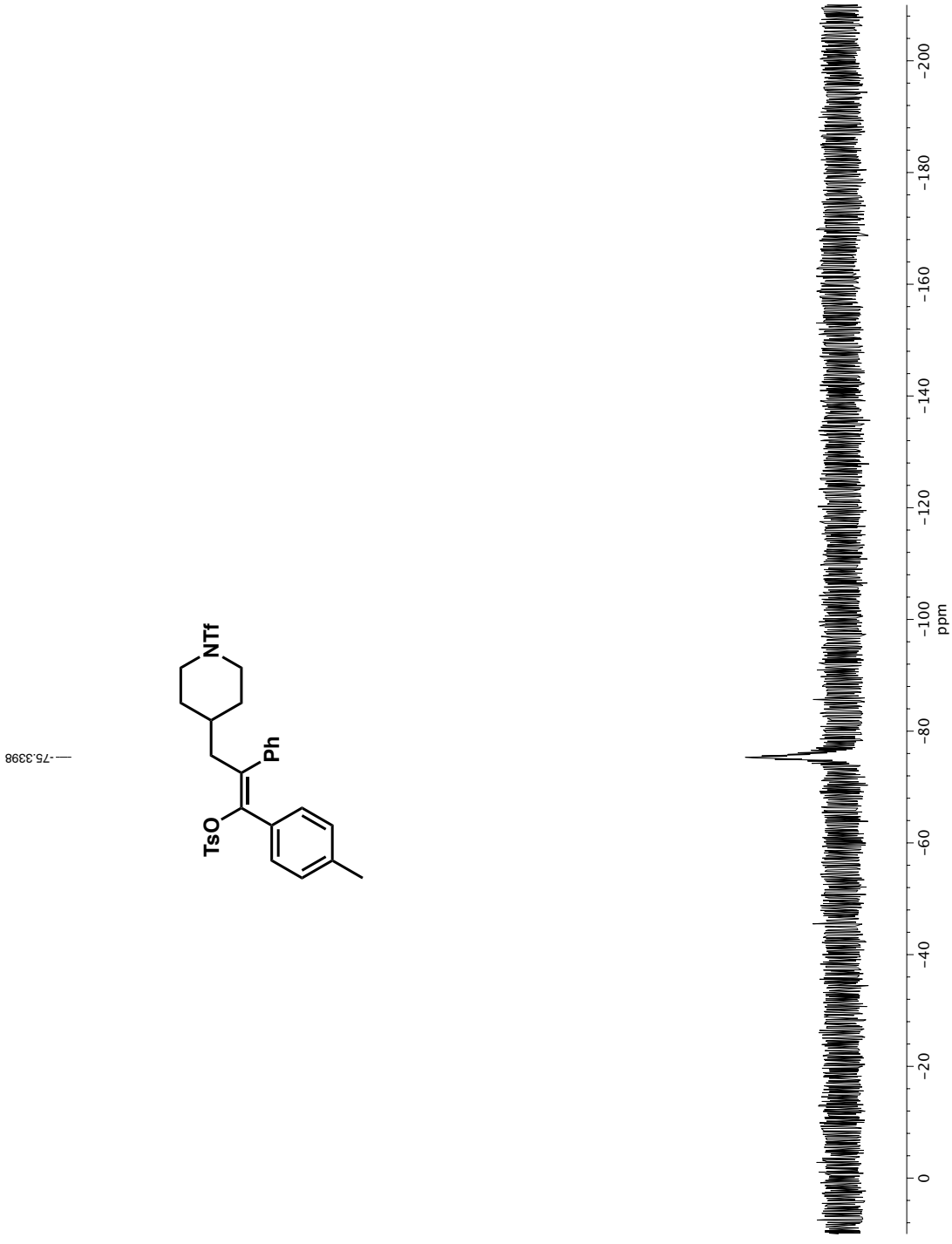
^{19}F NMR (282 MHz, $CDCl_3$) of **221**.



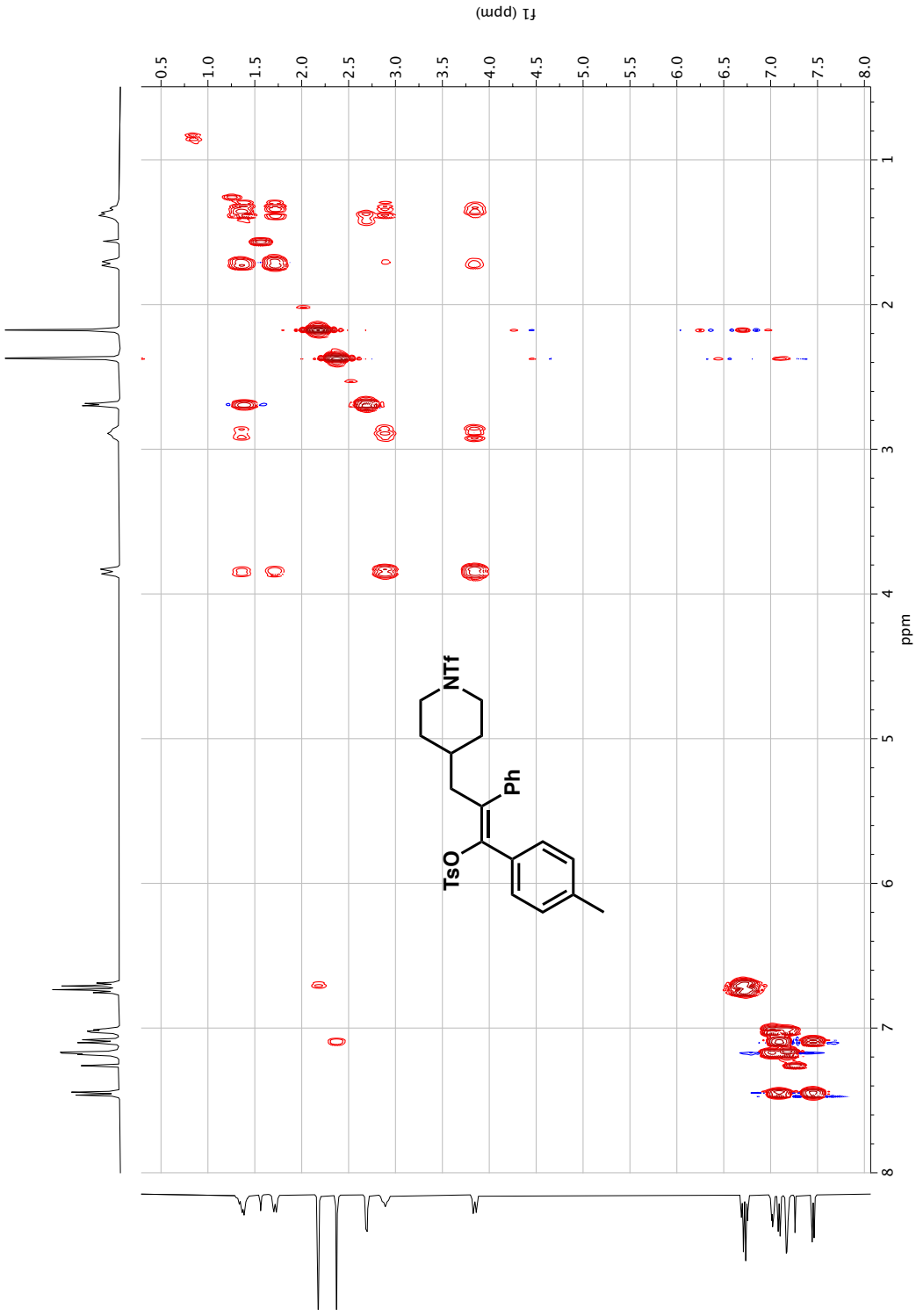
^{1}H NMR (300 MHz, $CDCl_3$) of **212a**.



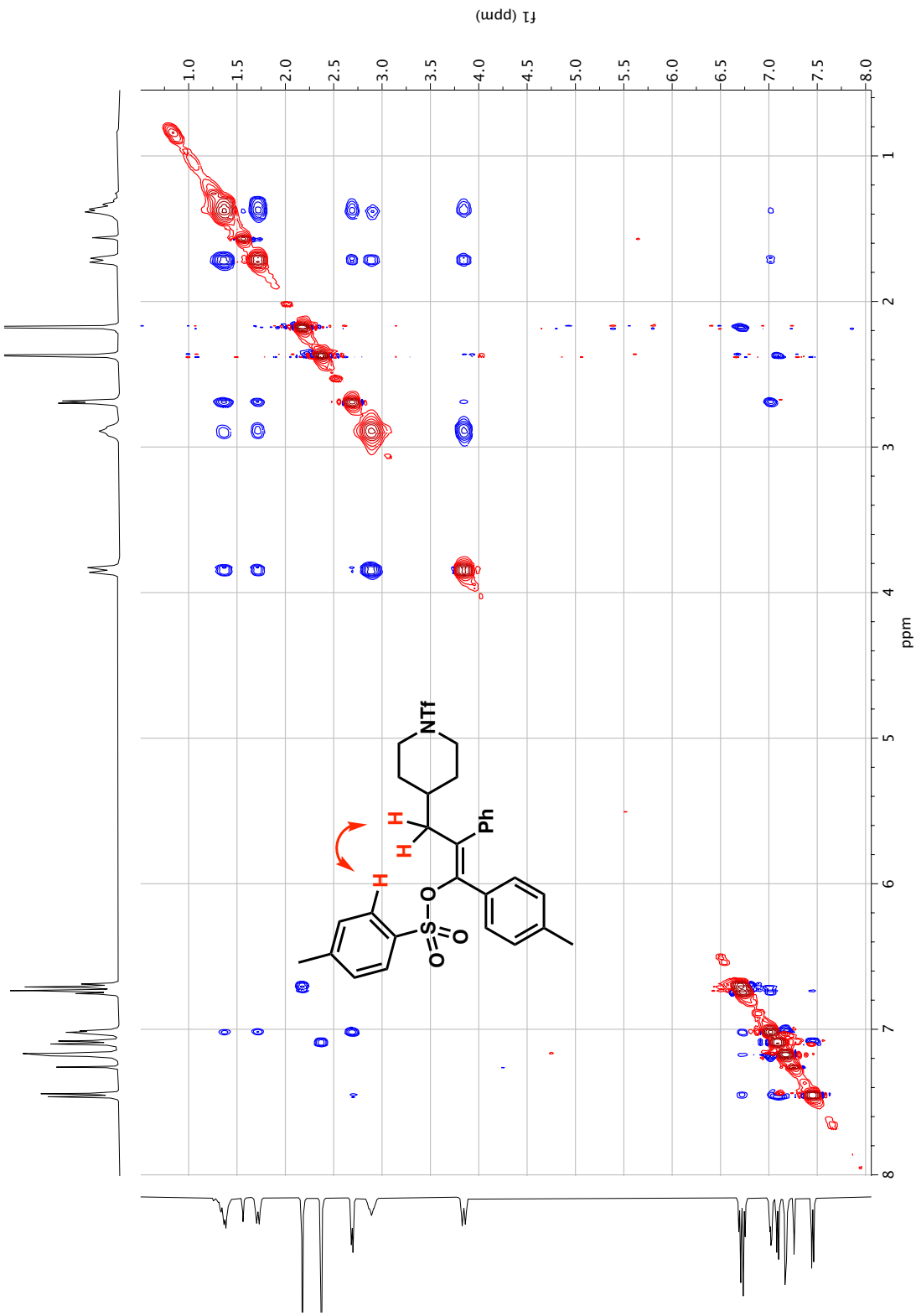
^{13}C NMR (101 MHz, $CDCl_3$) of **212a**.



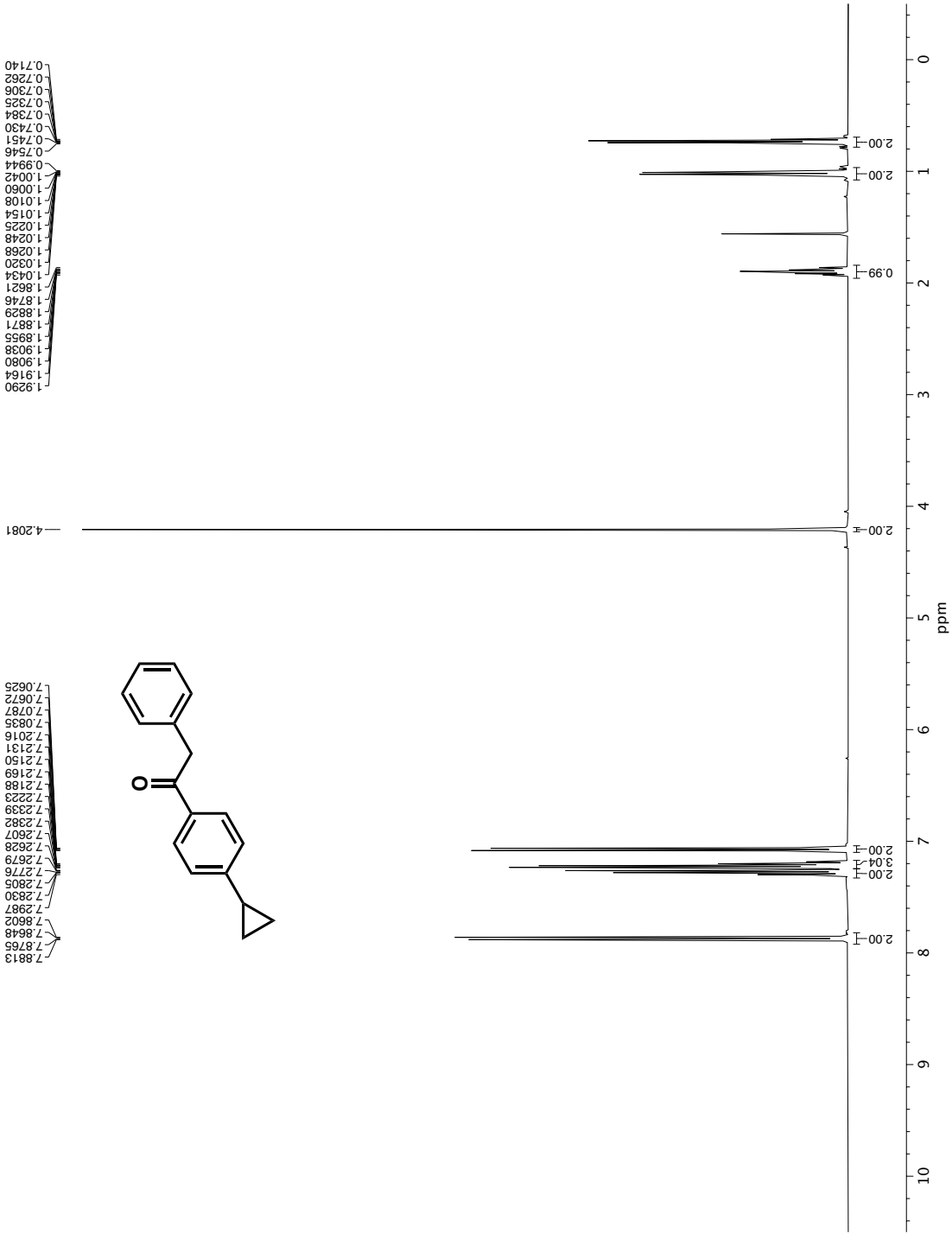
^{19}F NMR (282 MHz, $CDCl_3$) of **212a**.



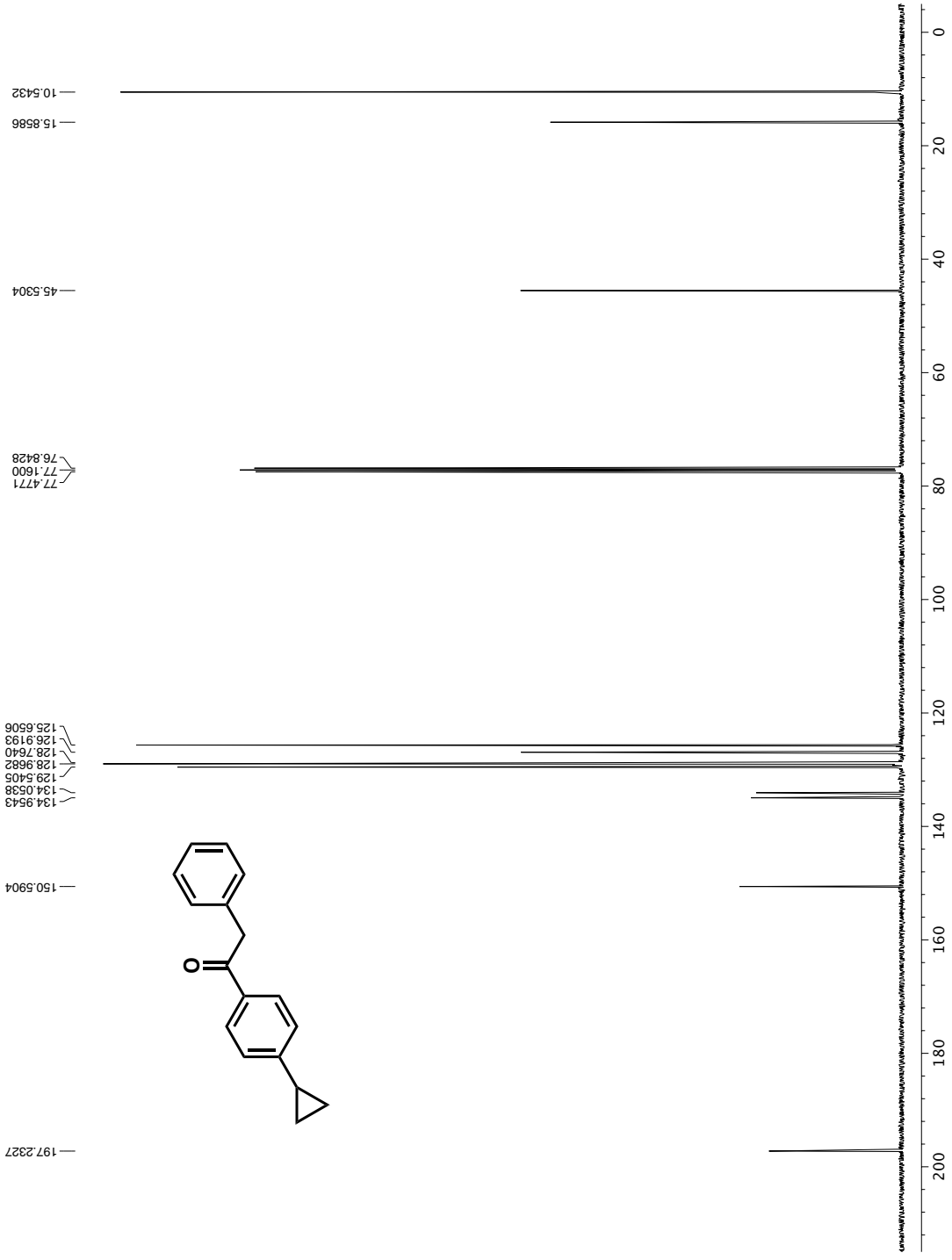
COSY NMR (400 MHz, $CDCl_3$) of **212a**.



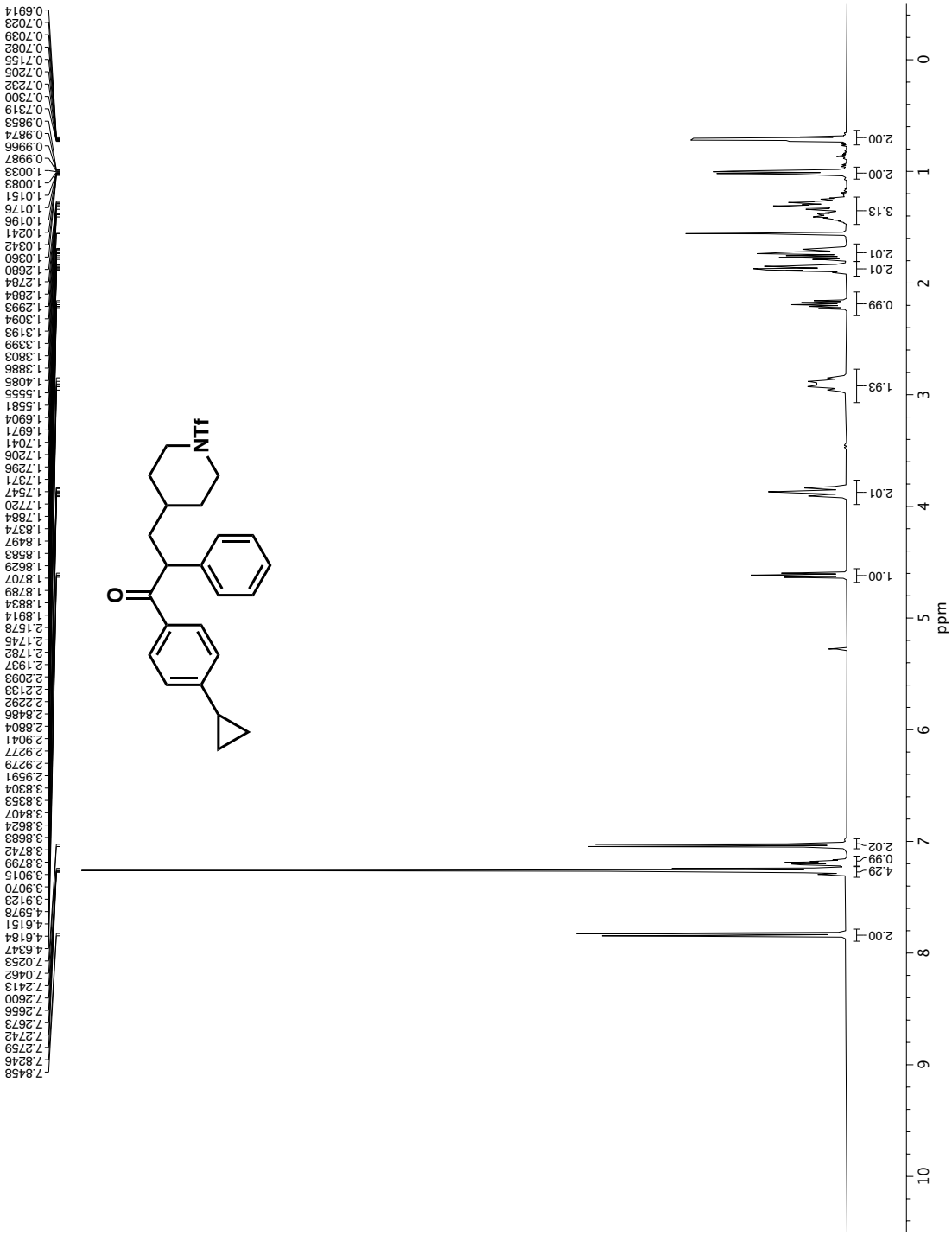
NOESY NMR (400 MHz, $CDCl_3$) of **212a**.



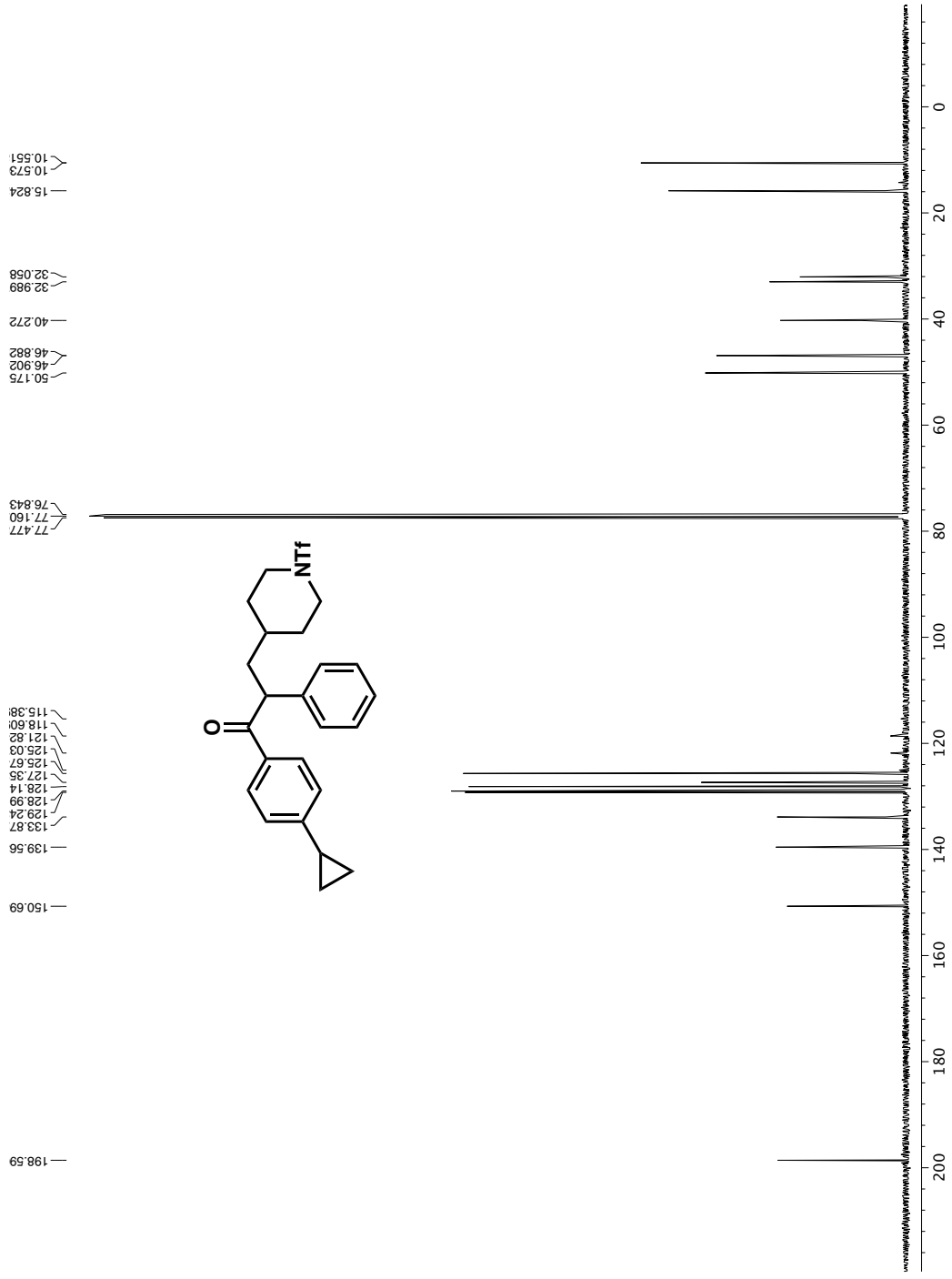
^{1}H NMR (400 MHz, $CDCl_3$) of **222**.



^{13}C NMR (101 MHz, $CDCl_3$) of **222**.

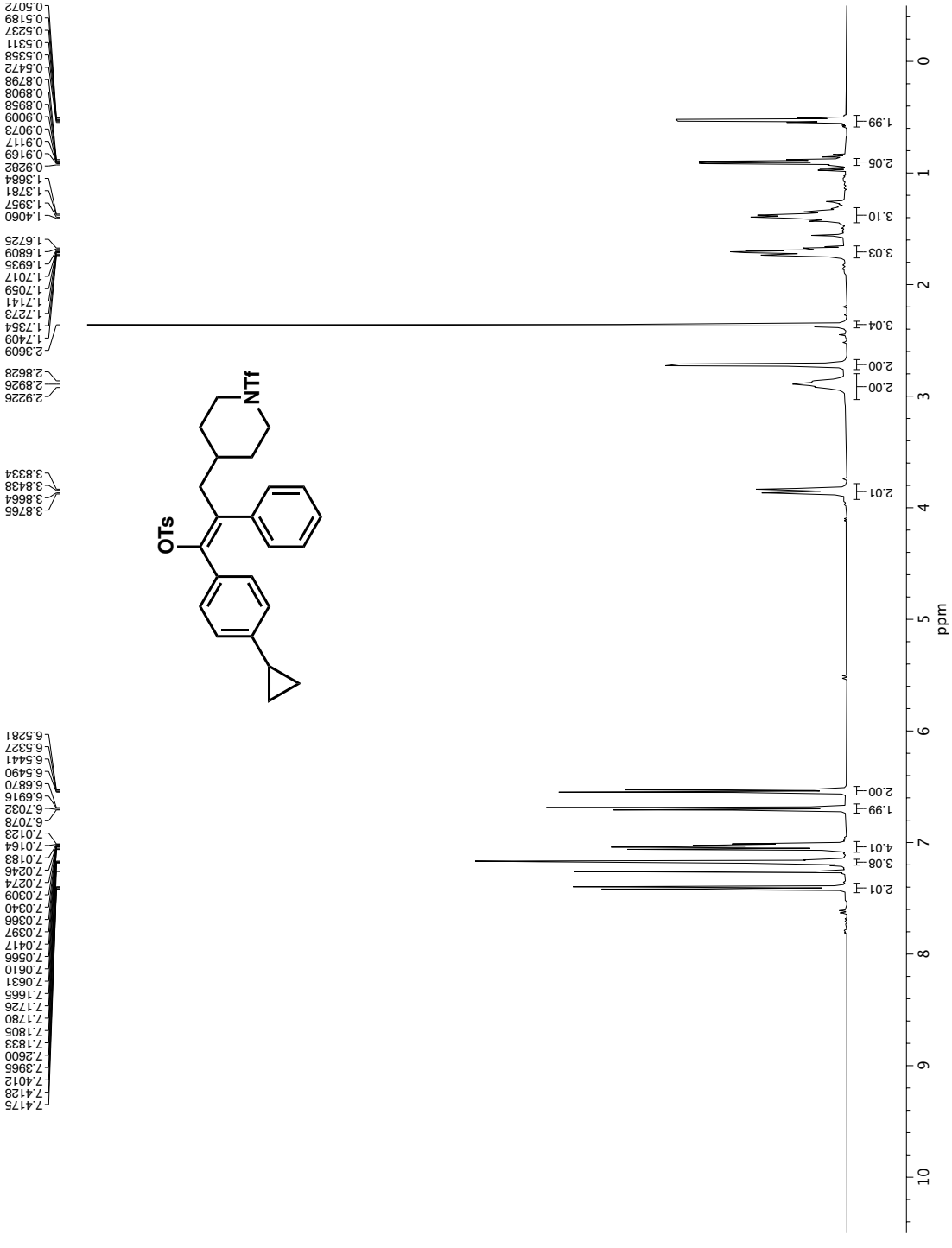


^{1}H NMR (400 MHz, $CDCl_3$) of **223**.

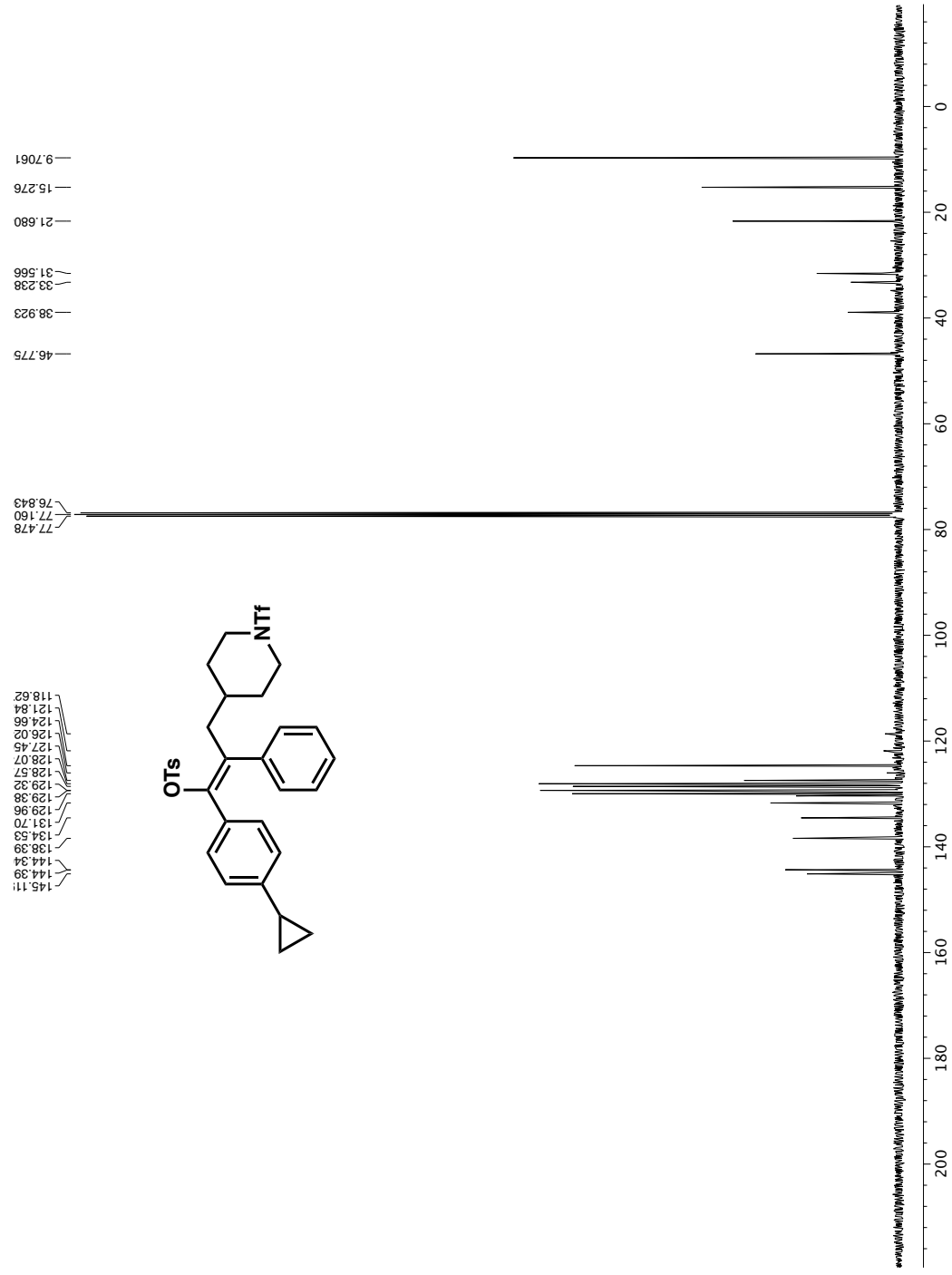


^{13}C NMR (101 MHz, $CDCl_3$) of **223**.

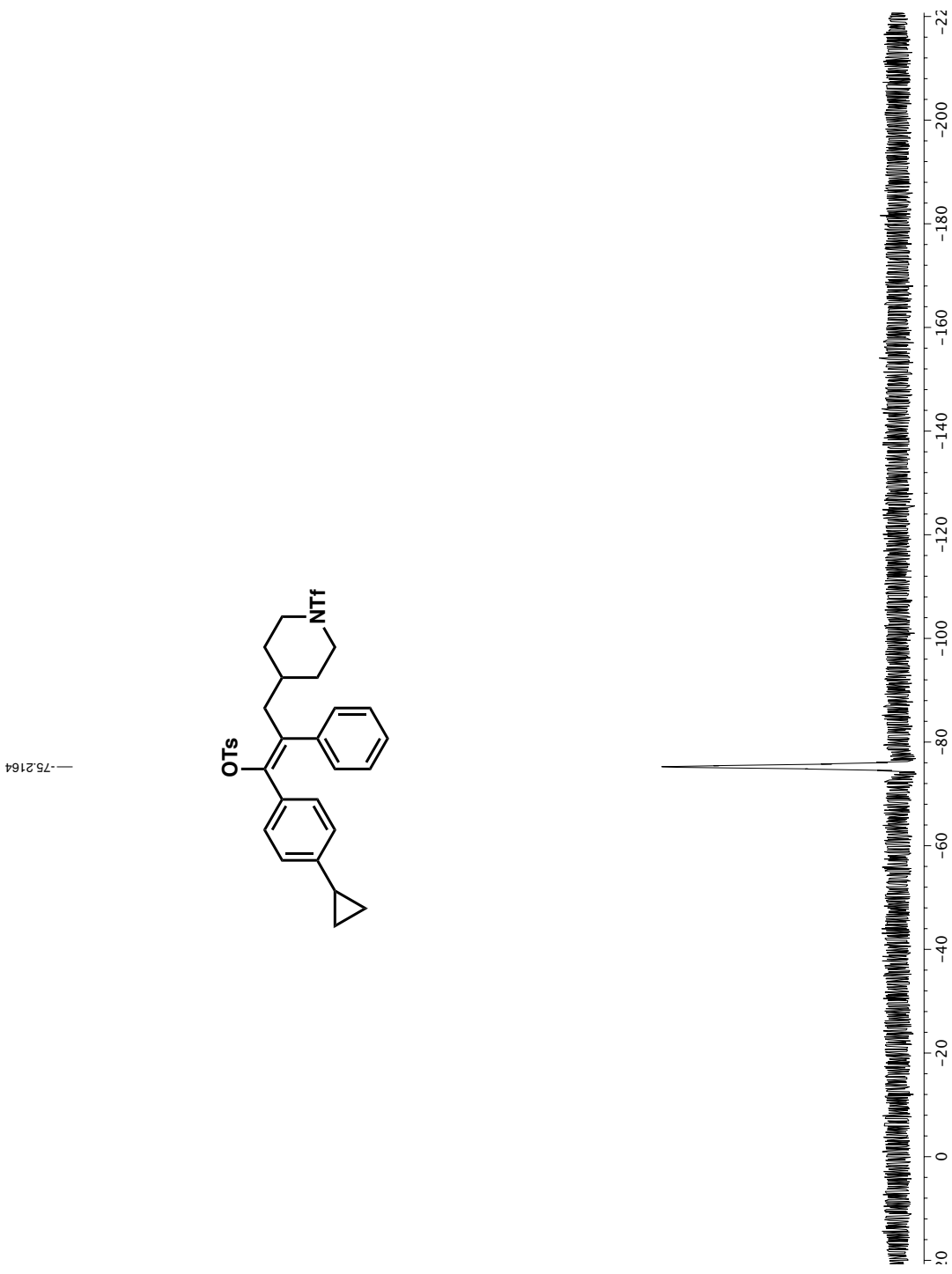
^{19}F NMR (376 MHz, $CDCl_3$) of **223**.



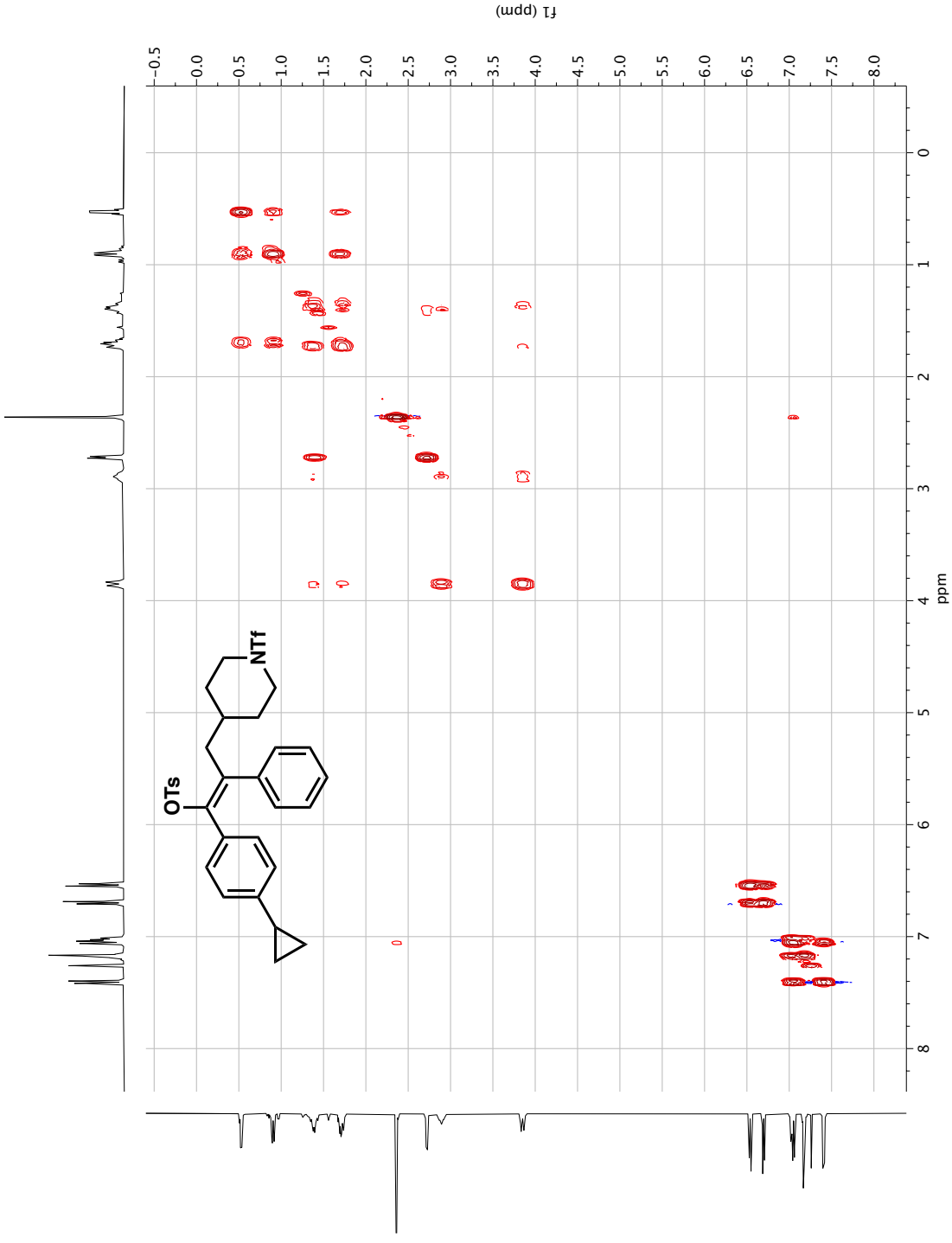
^{1}H NMR (400 MHz, $CDCl_3$) of **212b**.



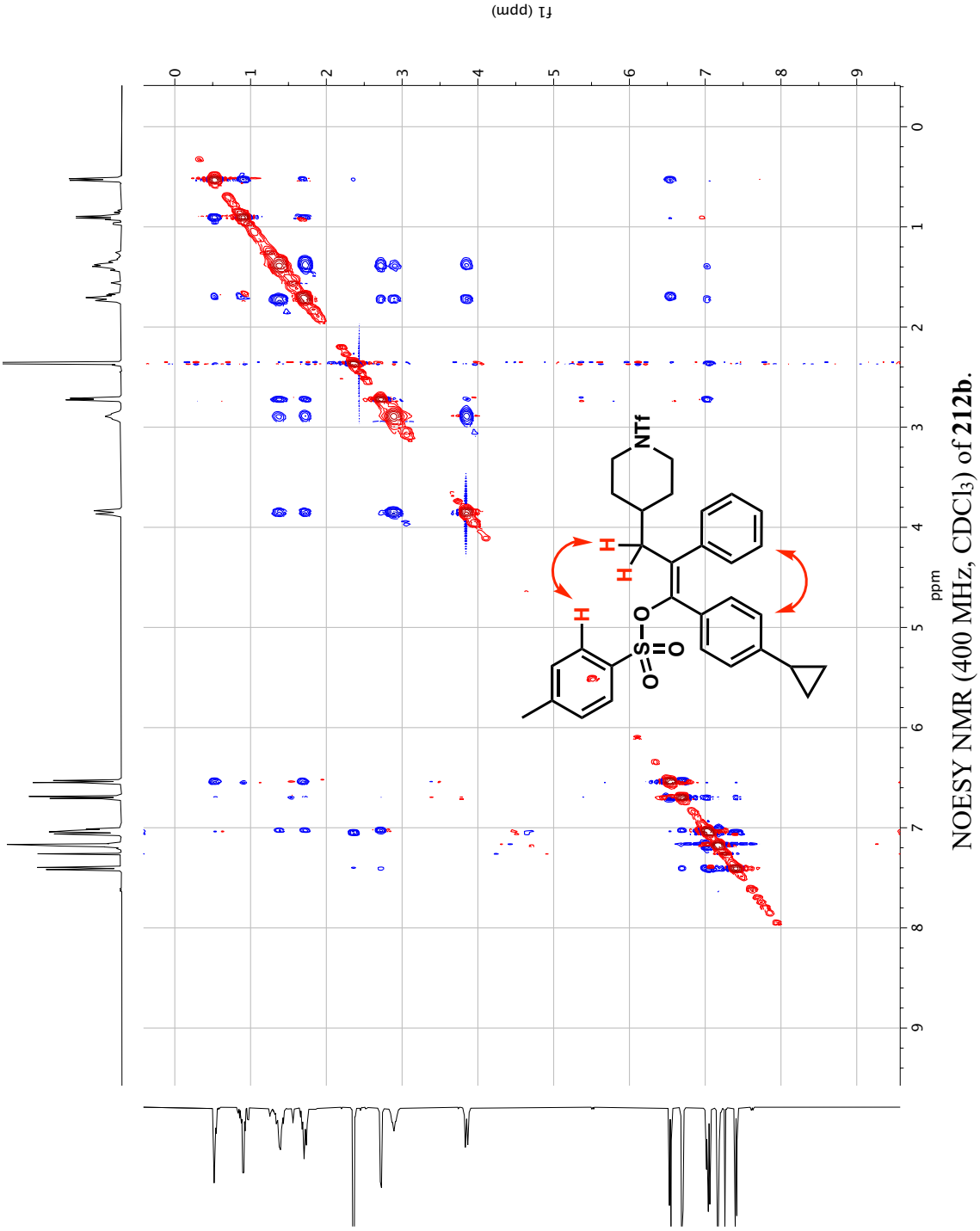
^{13}C NMR (101 MHz, $CDCl_3$) of **212b**.



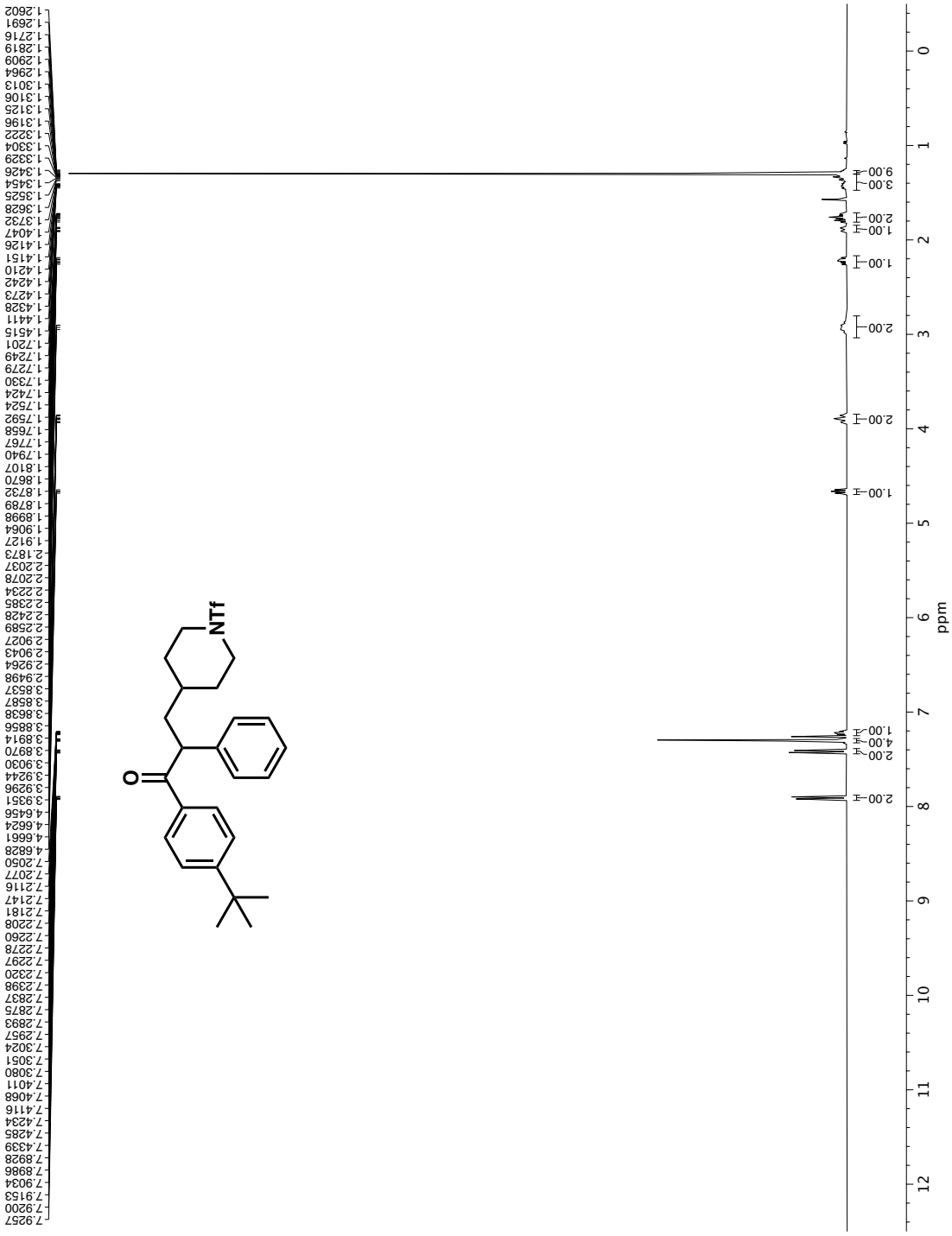
^{19}F NMR (376 MHz, $CDCl_3$) of **212b**.



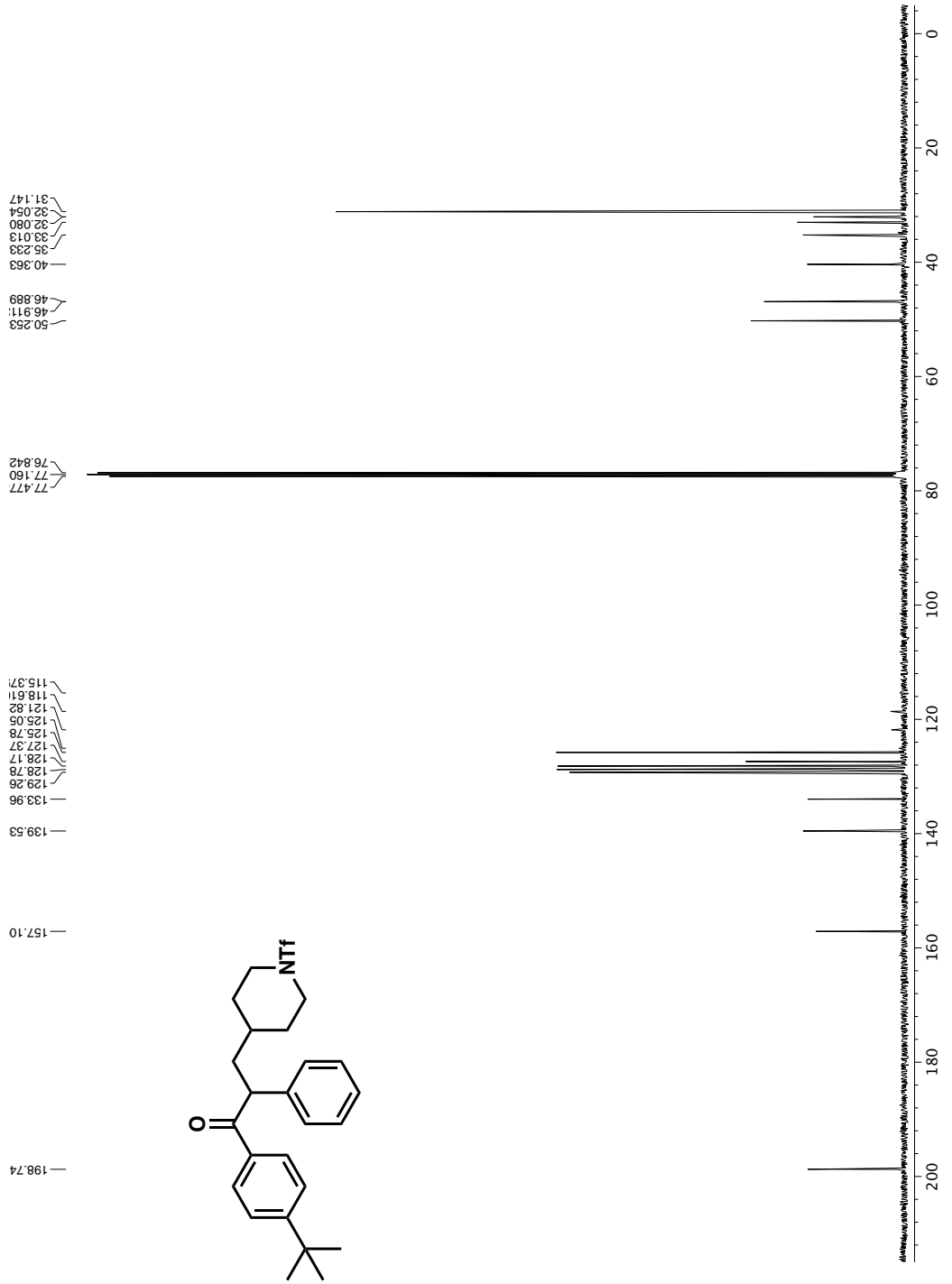
COSY NMR (400 MHz, $CDCl_3$) of **212b**.



NOESY NMR (400 MHz, $CDCl_3$) of **212b**.

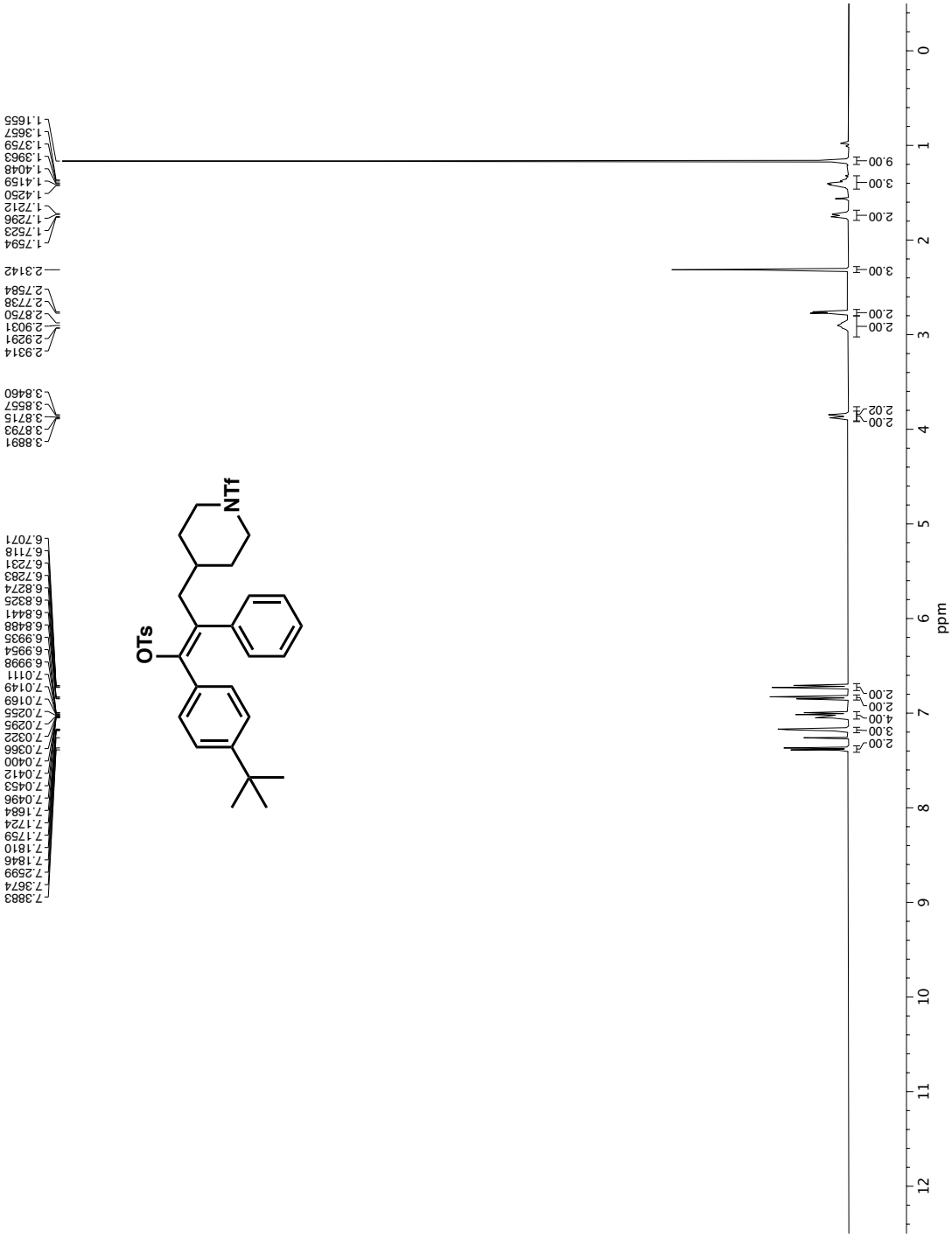


^{1}H NMR (400 MHz, $CDCl_3$) of **225**.

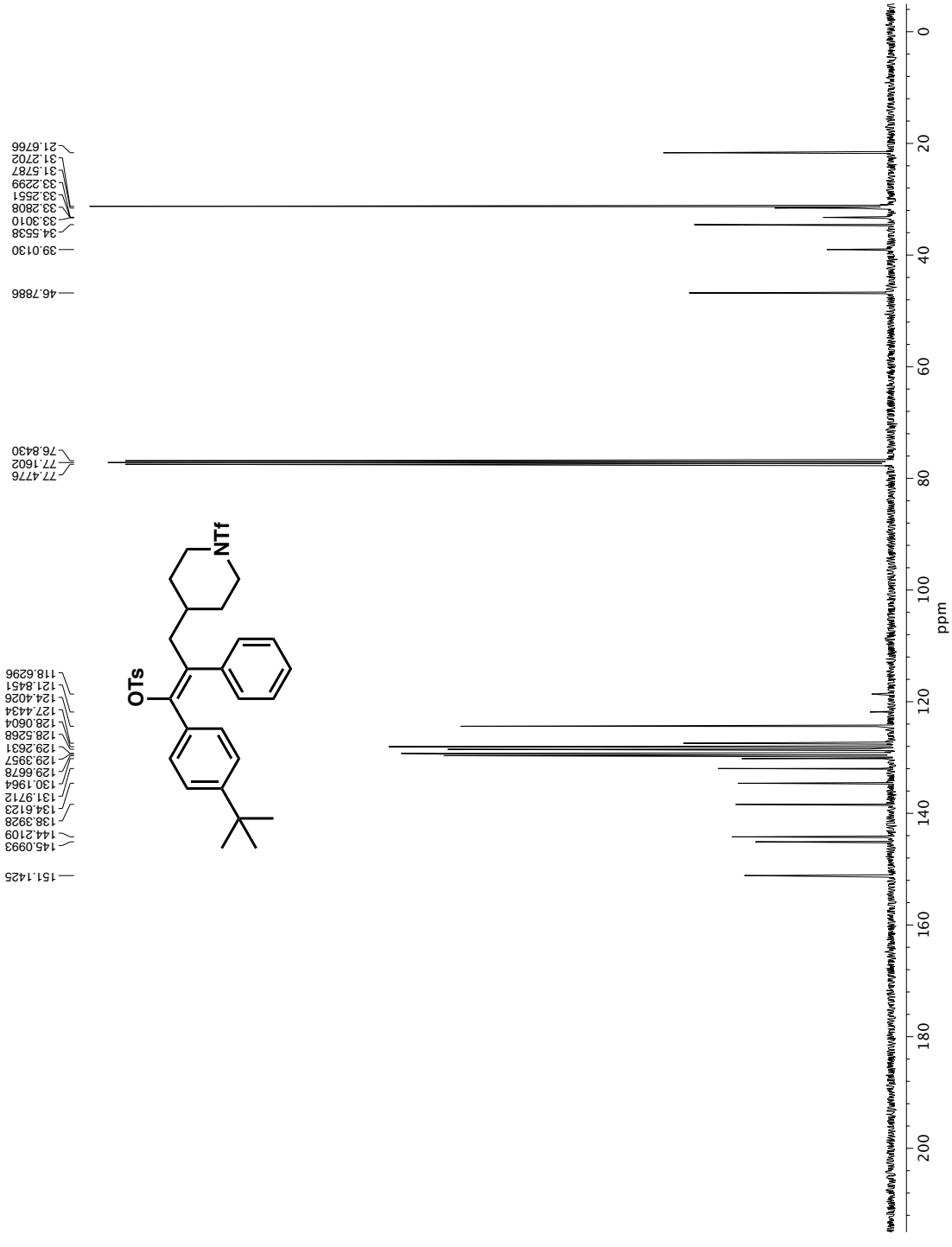


^{13}C NMR (101 MHz, $CDCl_3$) of **225**.

^{19}F NMR (376 MHz, $CDCl_3$) of **225**.

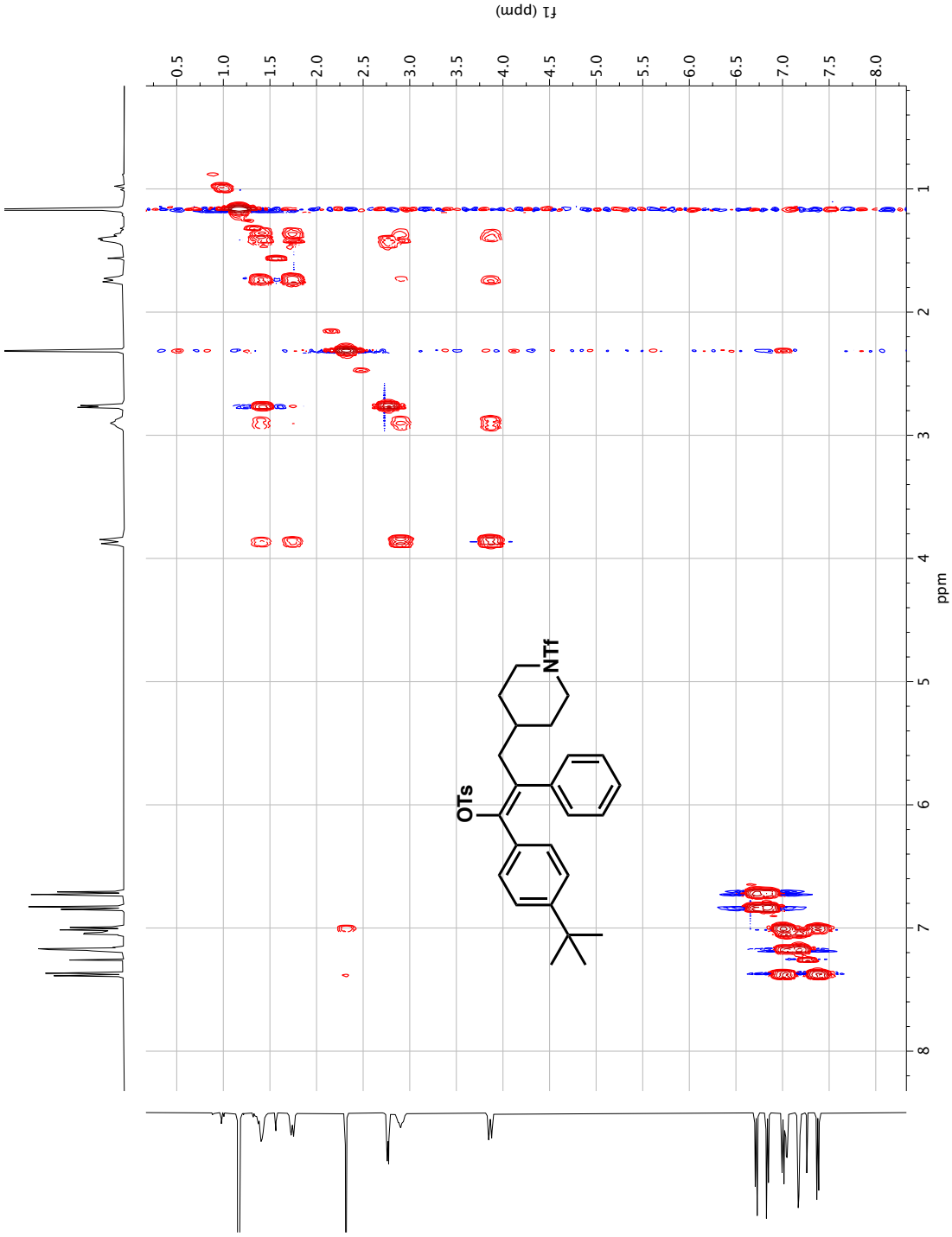


^{1}H NMR (400 MHz, $CDCl_3$) of **212c**.

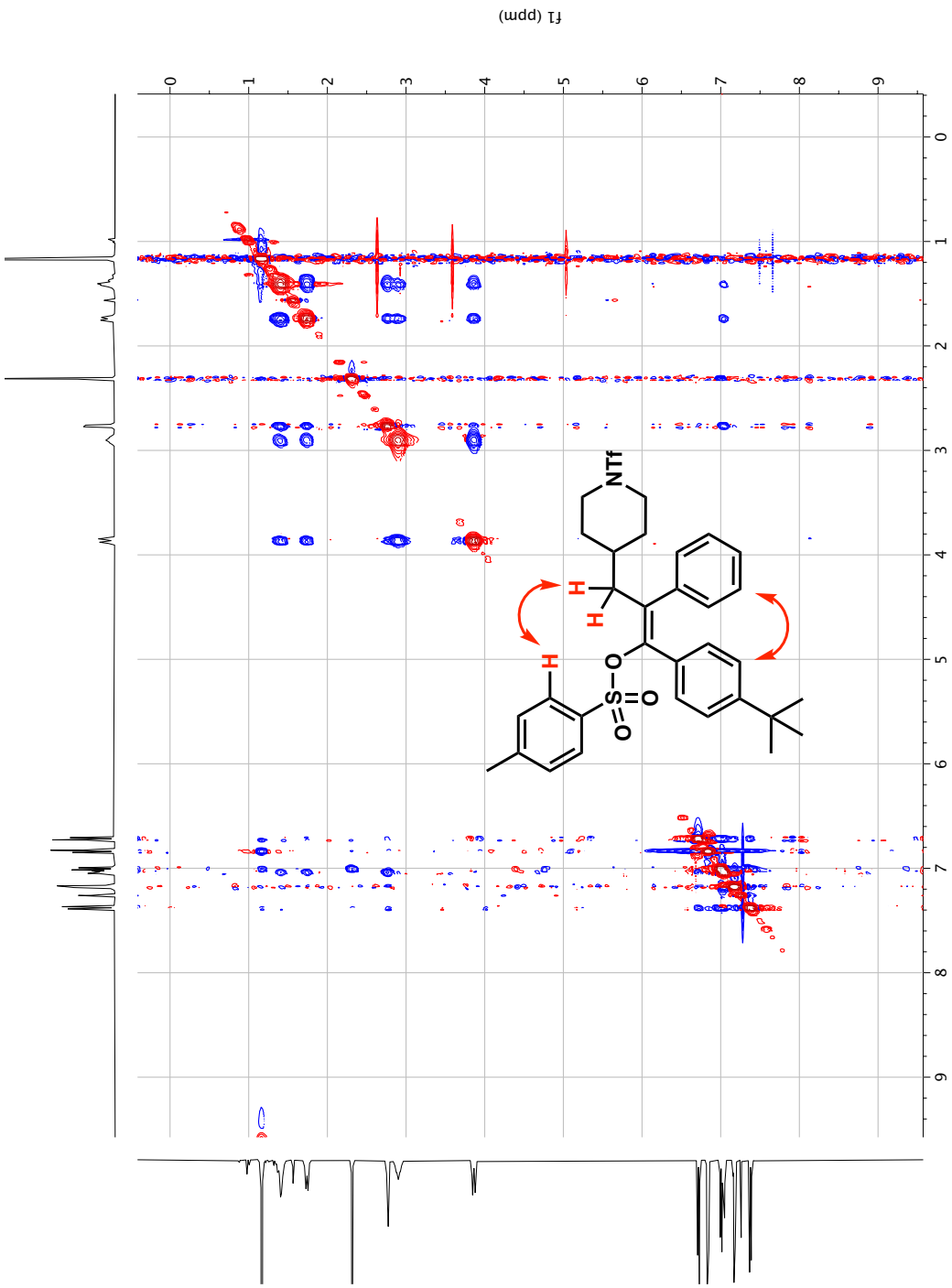


^{13}C NMR (101 MHz, $CDCl_3$) of **212c**.

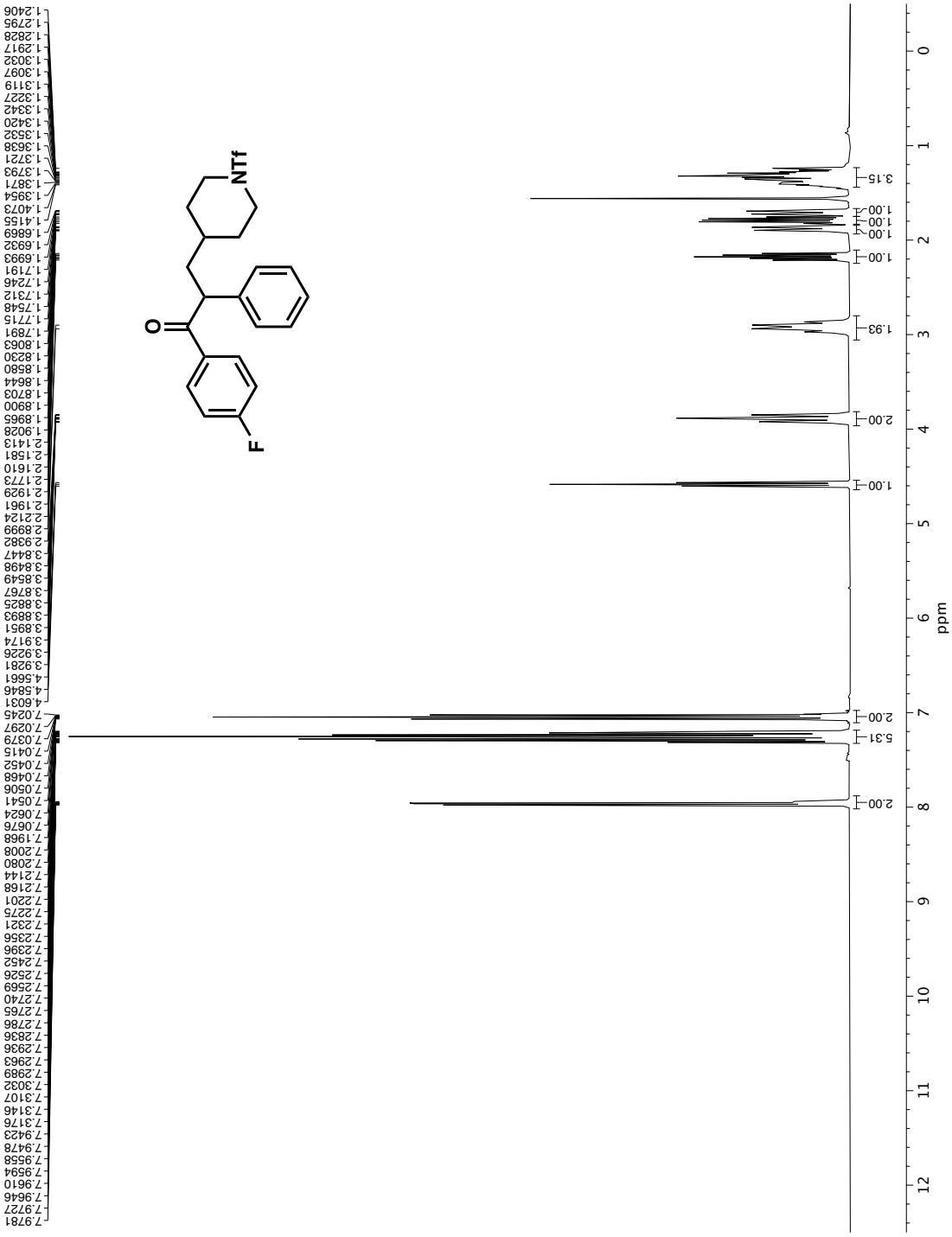
^{19}F NMR (376 MHz, $CDCl_3$) of **212c**.



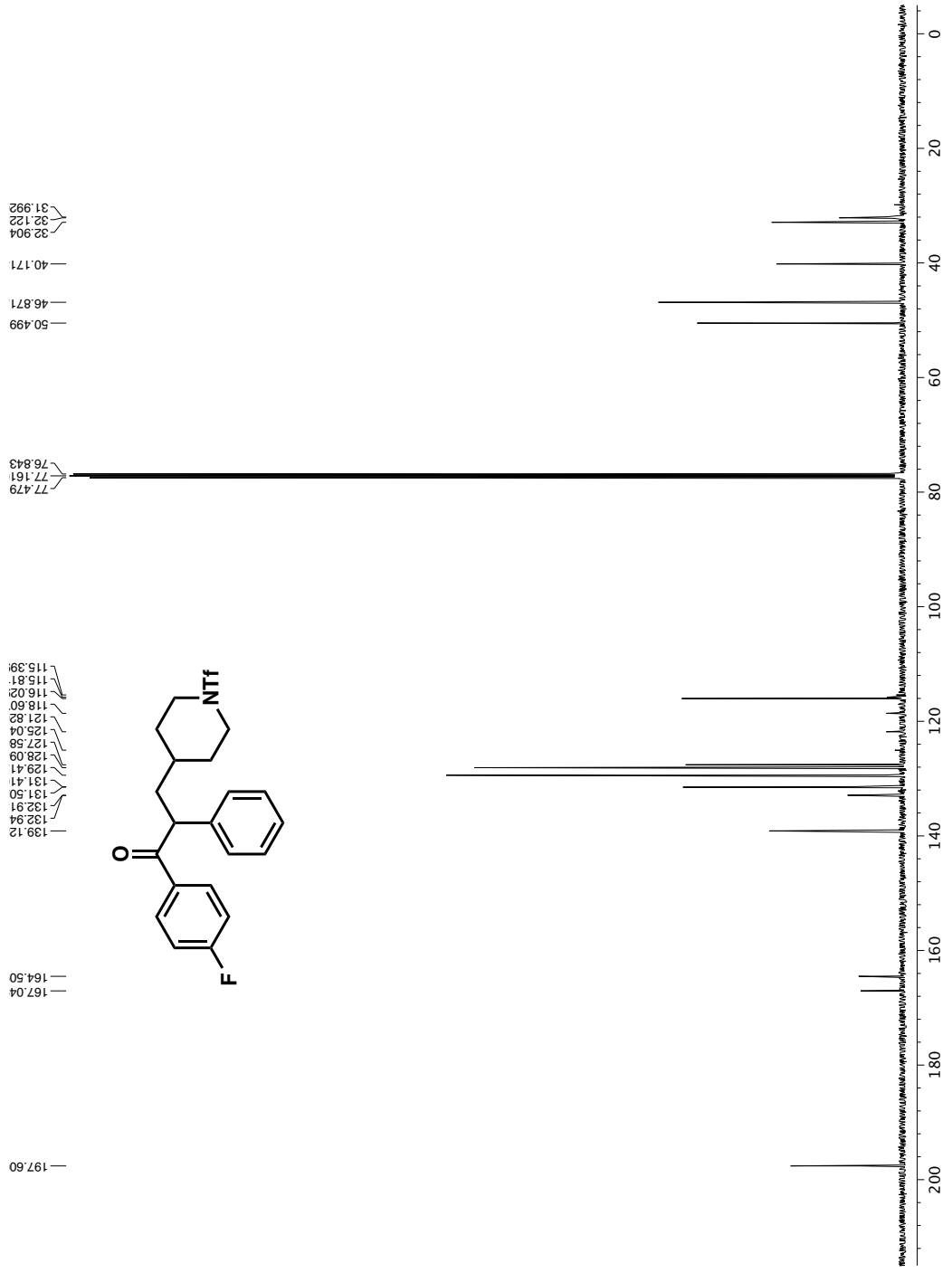
COSY NMR (400 MHz, $CDCl_3$) of **212c**.



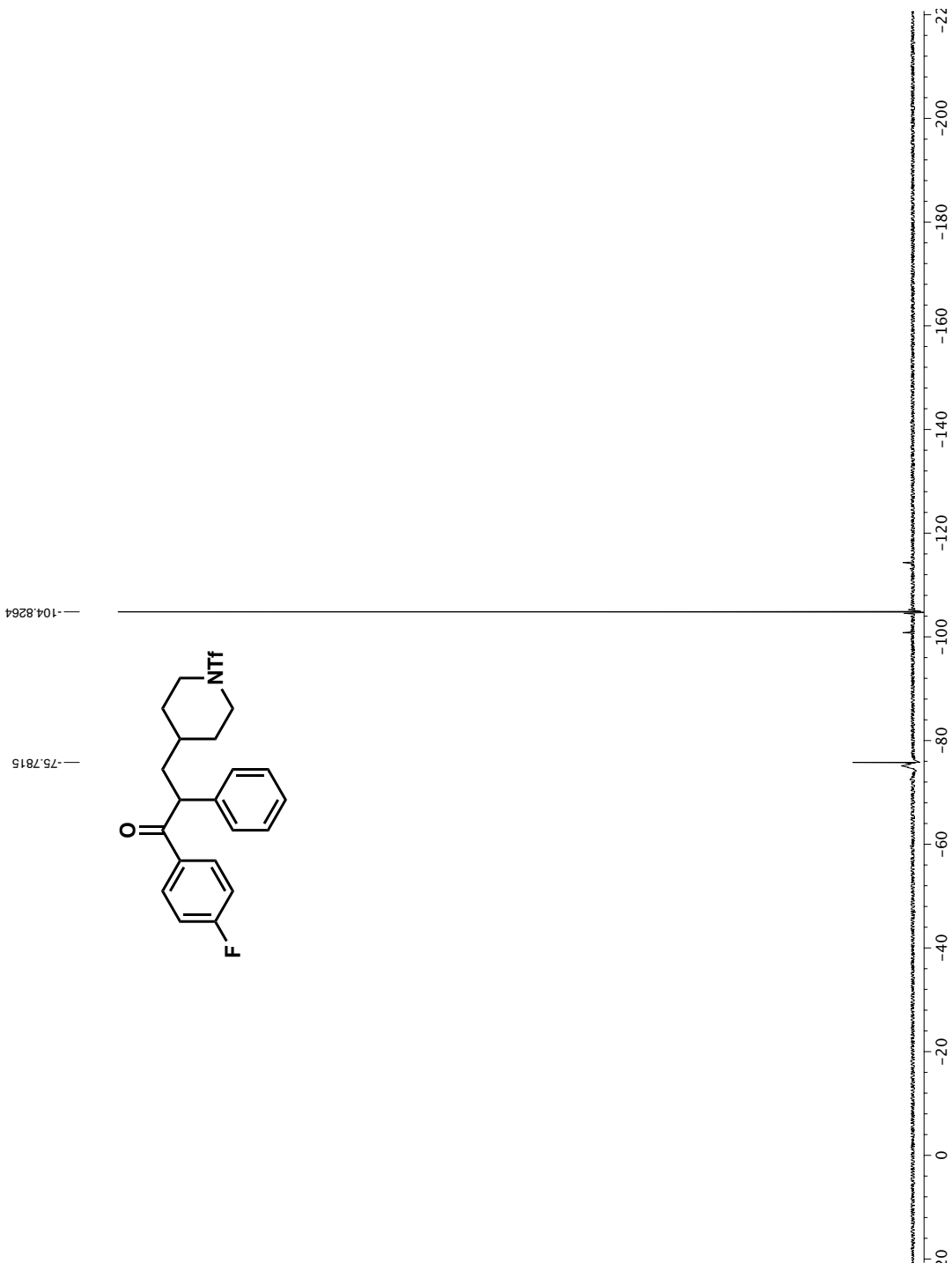
NOESY NMR (400 MHz, $CDCl_3$) of **212c**.



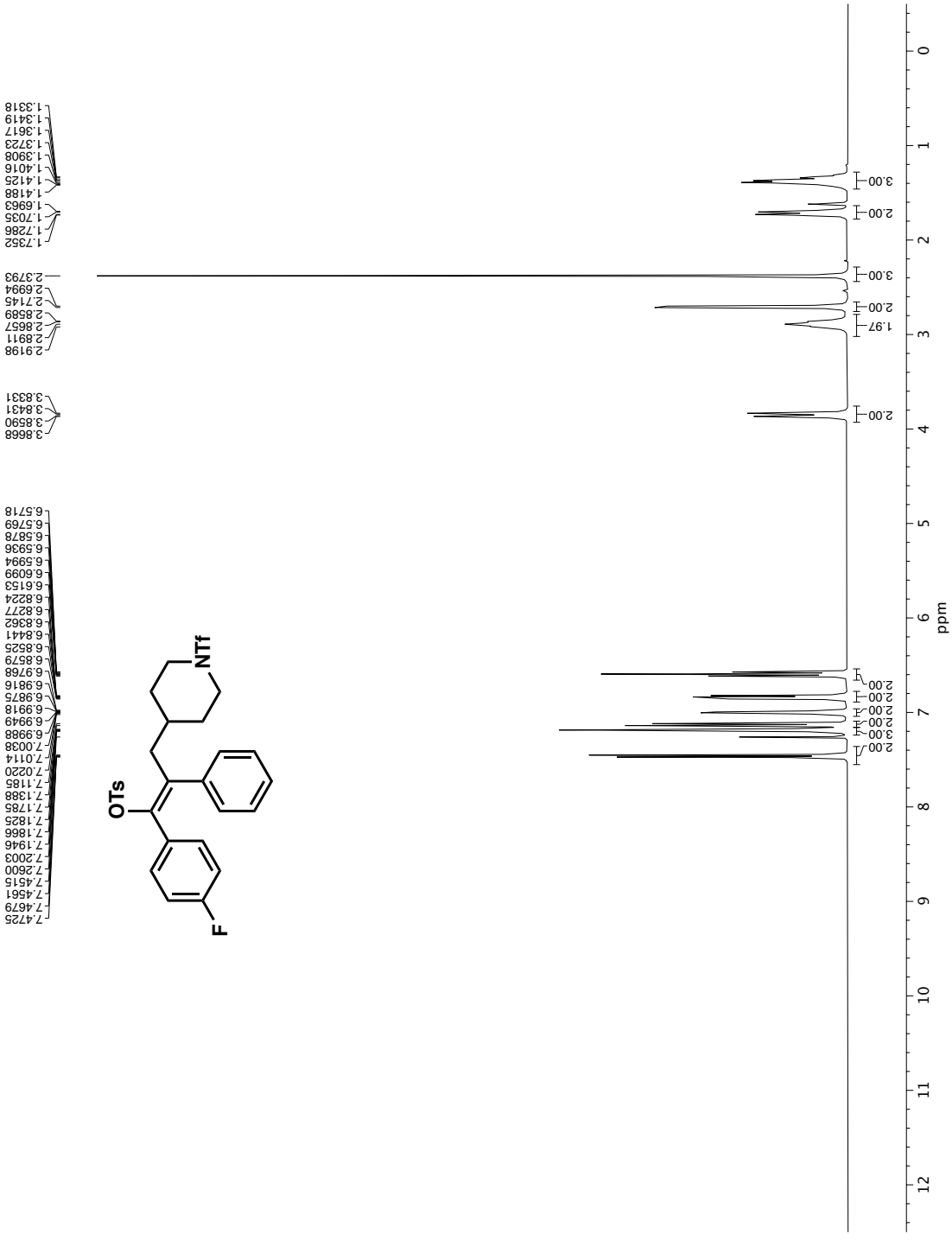
^{1}H NMR (400 MHz, $CDCl_3$) of **227**.



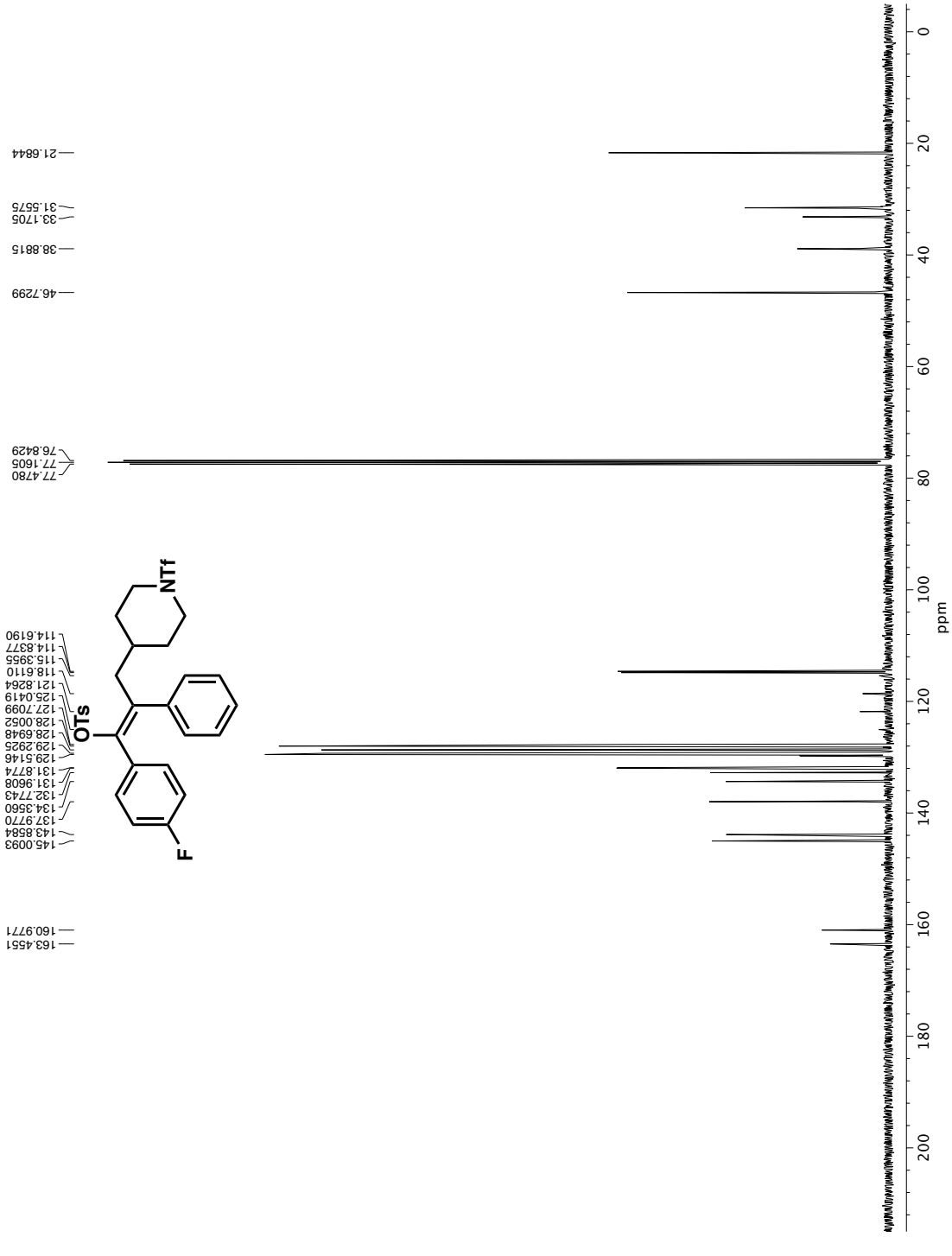
^{13}C NMR (101 MHz, $CDCl_3$) of **227**.



^{19}F NMR (376 MHz, $CDCl_3$) of **227**.

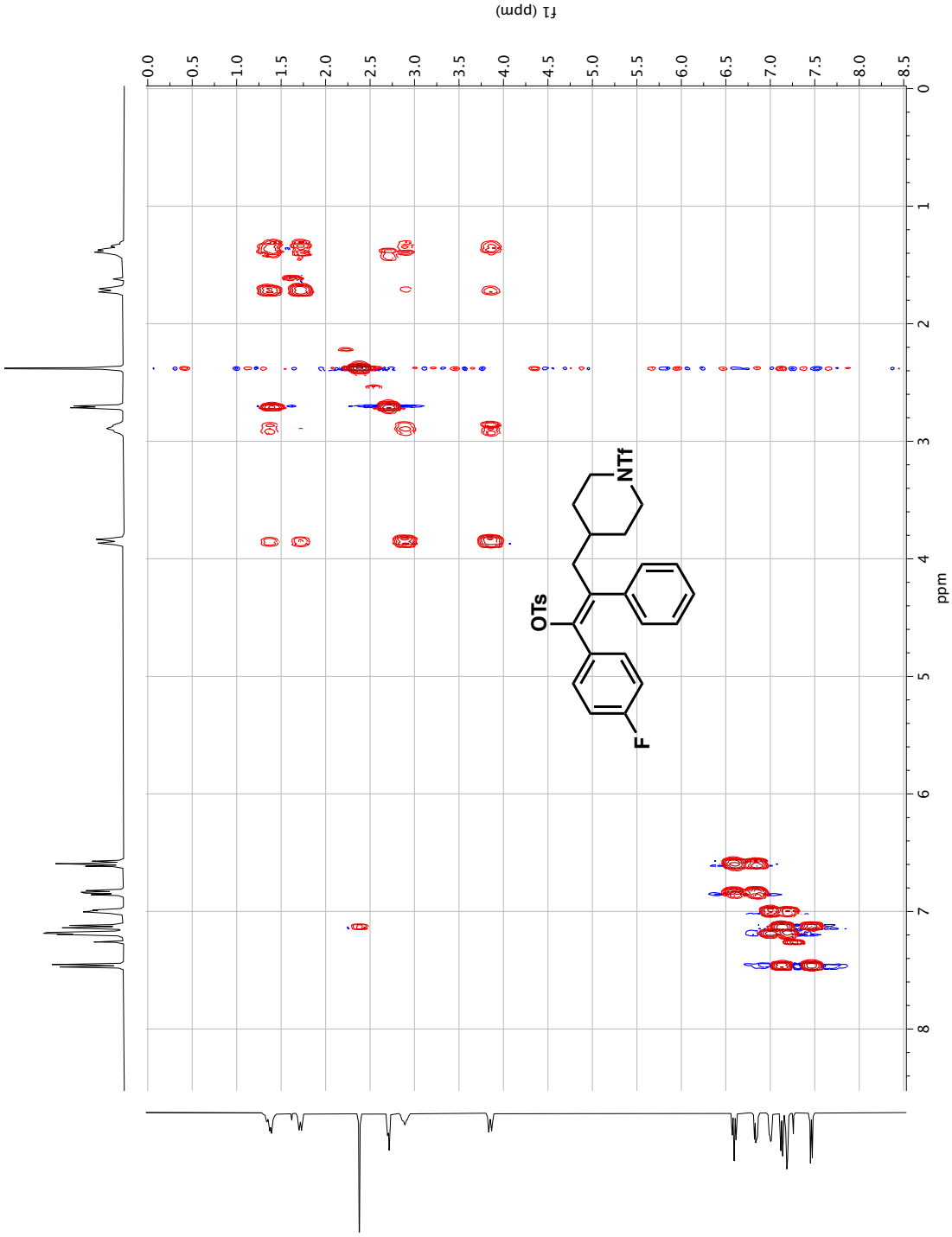


^{1}H NMR (400 MHz, $CDCl_3$) of **212d**.

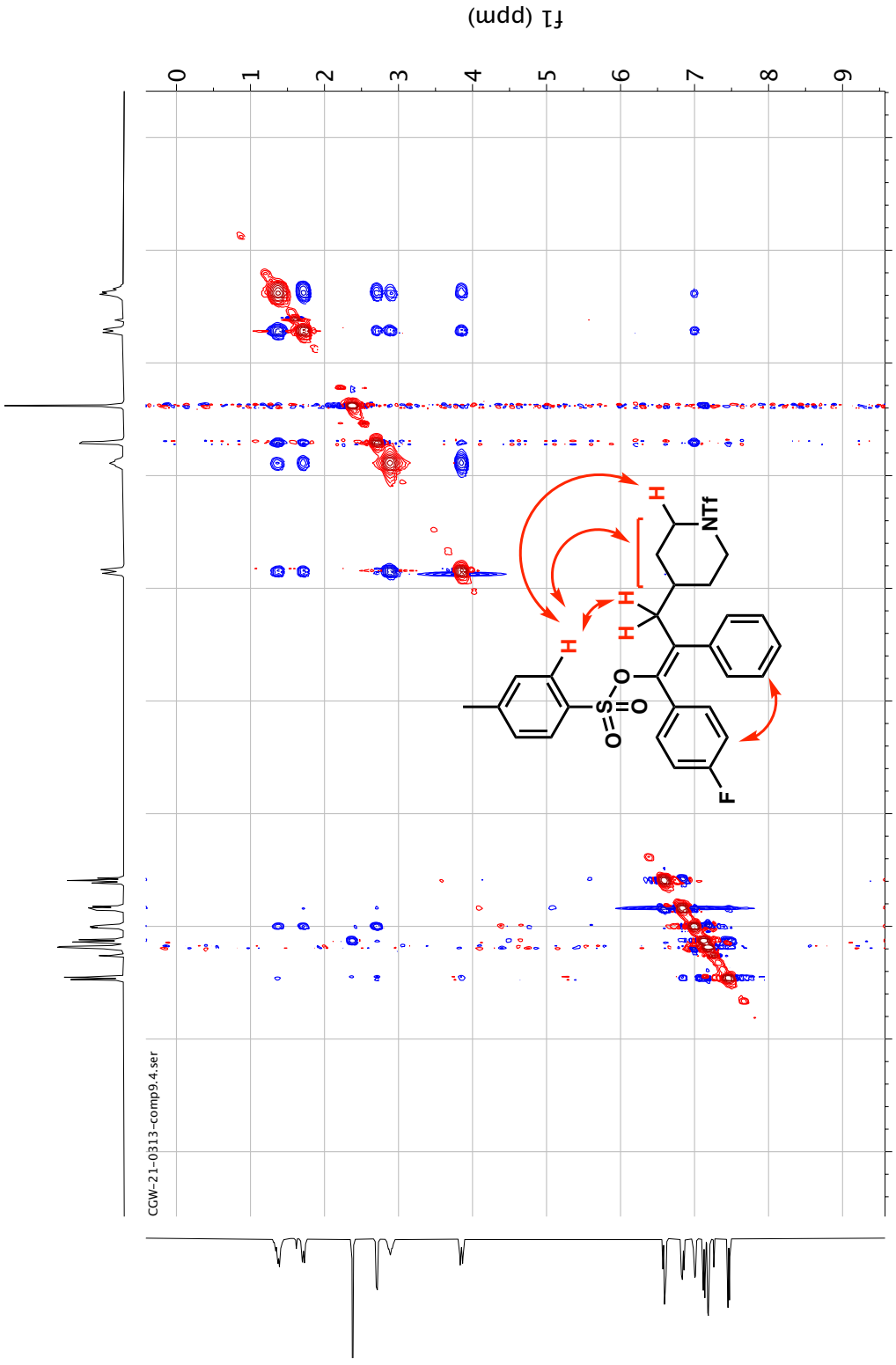


^{13}C NMR (101 MHz, $CDCl_3$) of **212d**.

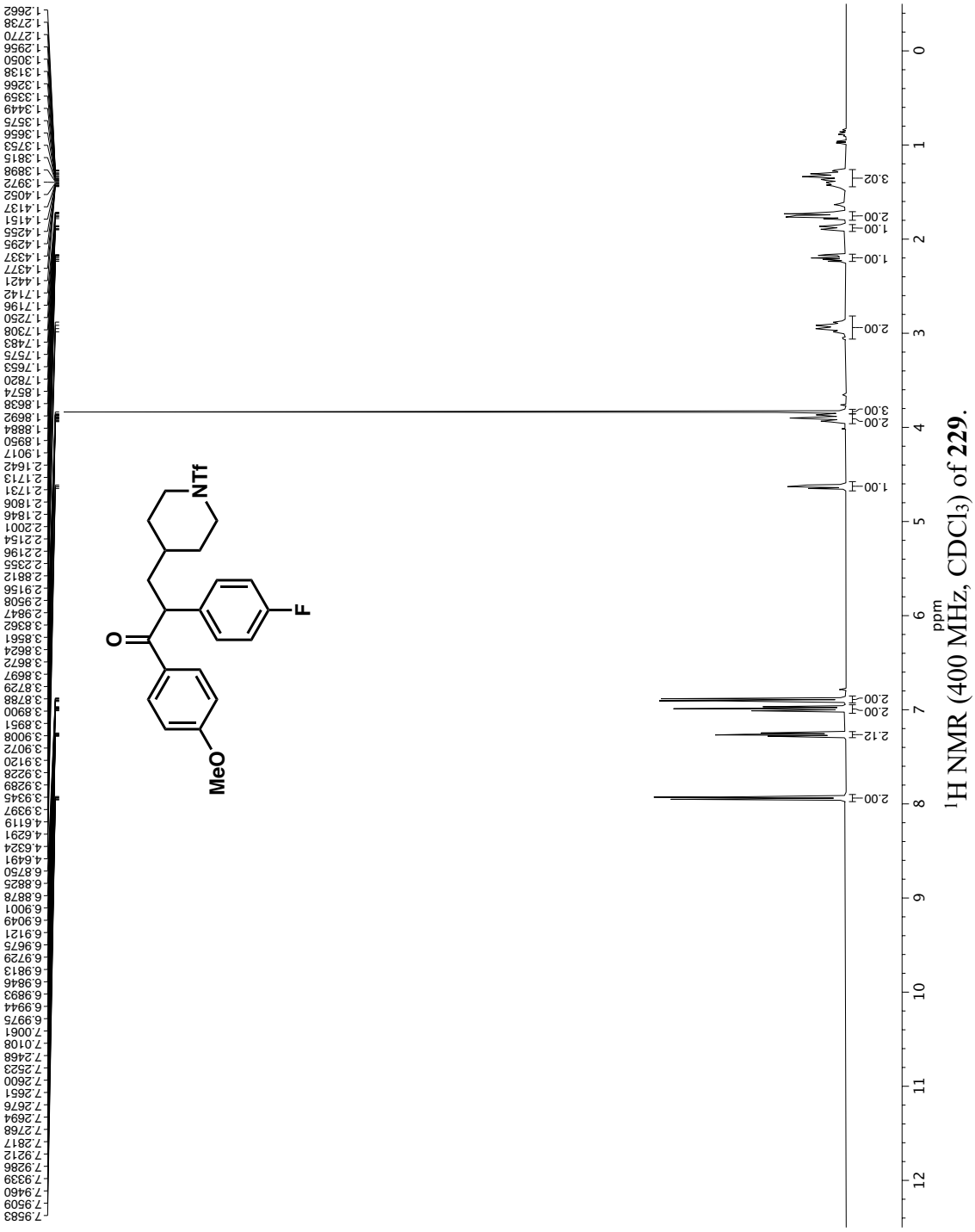
^{19}F NMR (376 MHz, $CDCl_3$) of **212d**.



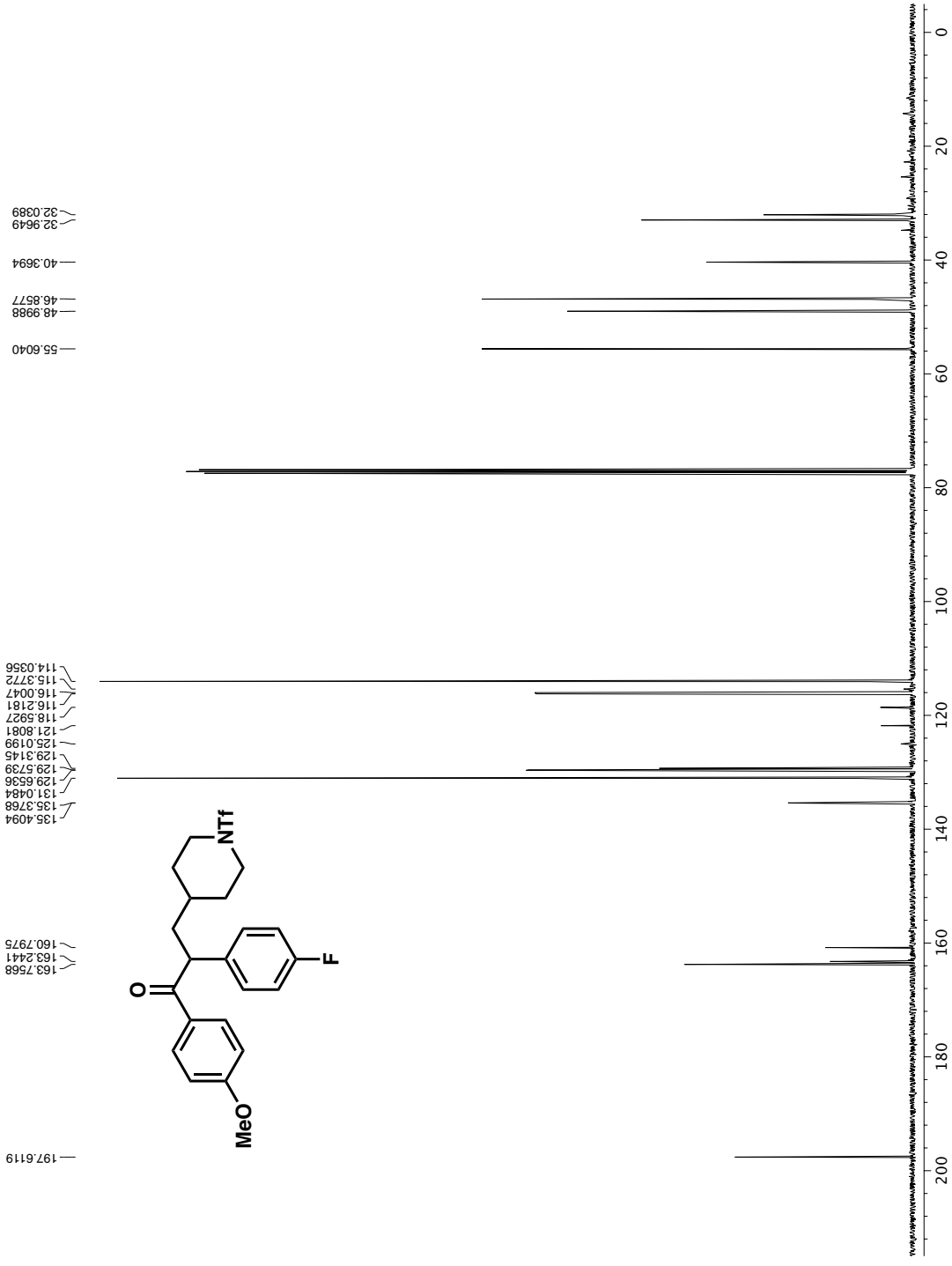
COSY NMR (400 MHz, $CDCl_3$) of **212d**.



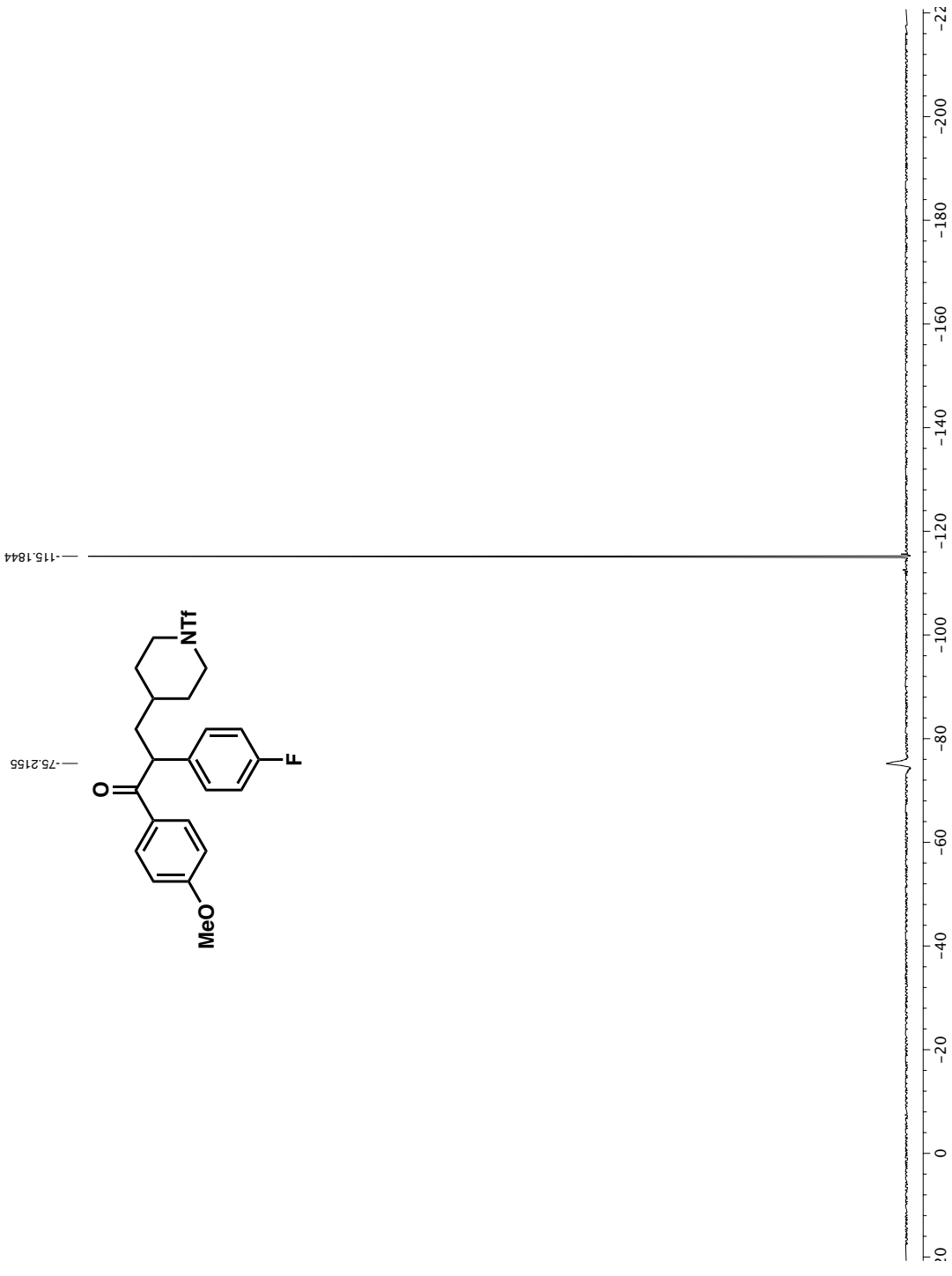
NOESY NMR (400 MHz, $CDCl_3$) of **212d**.



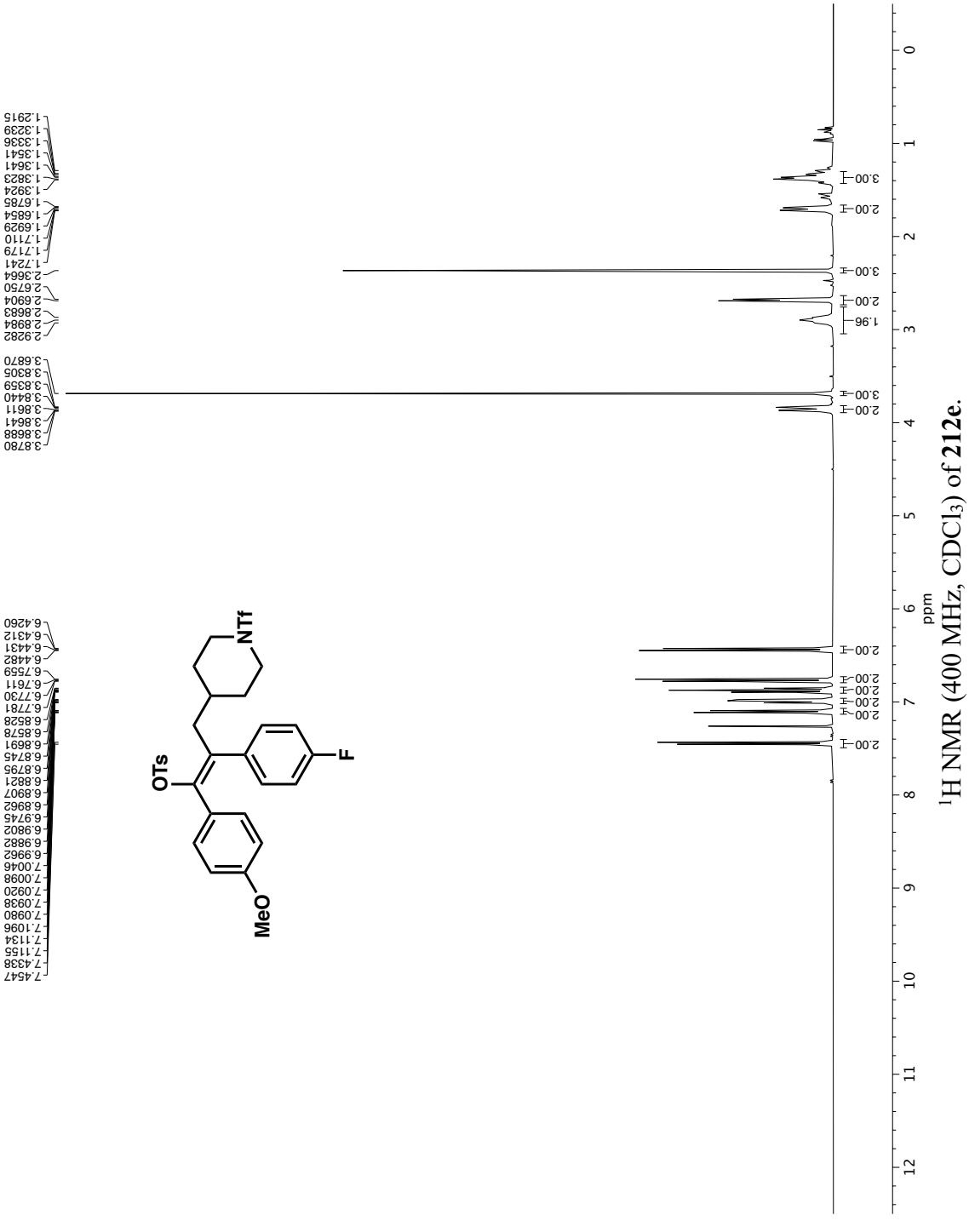
^{1}H NMR (400 MHz, $CDCl_3$) of **229**.



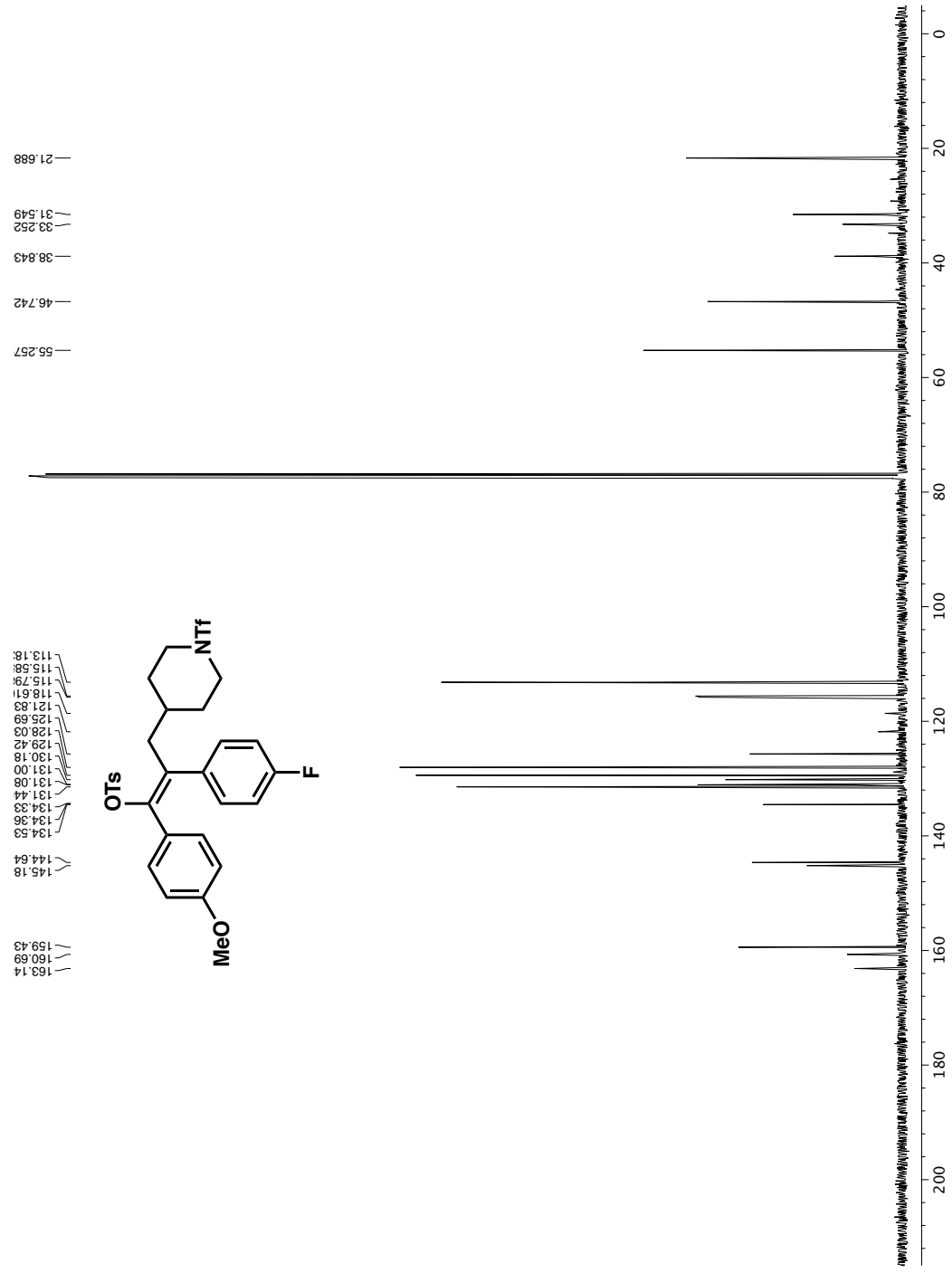
^{13}C NMR (101 MHz, $CDCl_3$) of **229**.



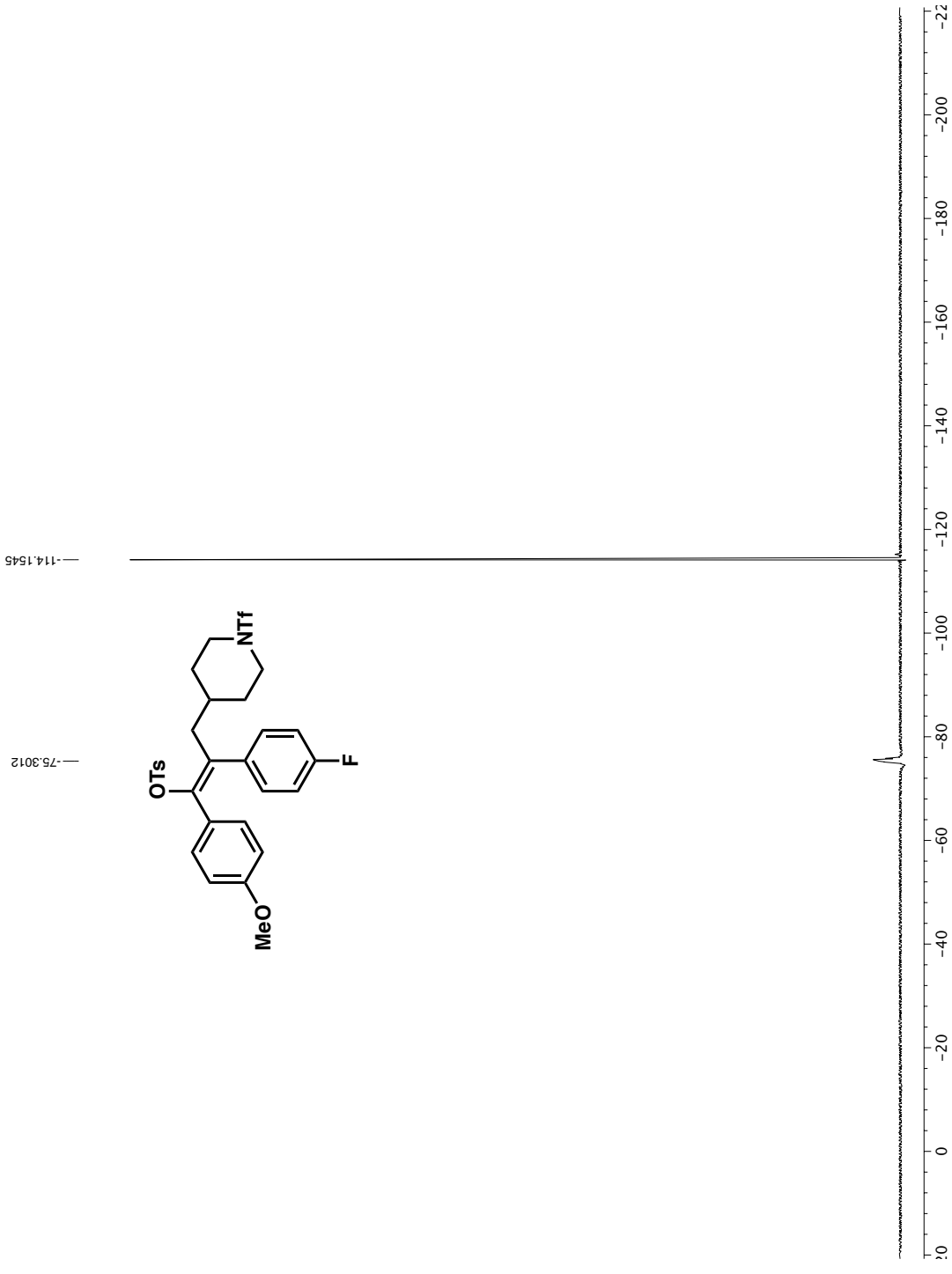
^{19}F NMR (376 MHz, $CDCl_3$) of **229**.



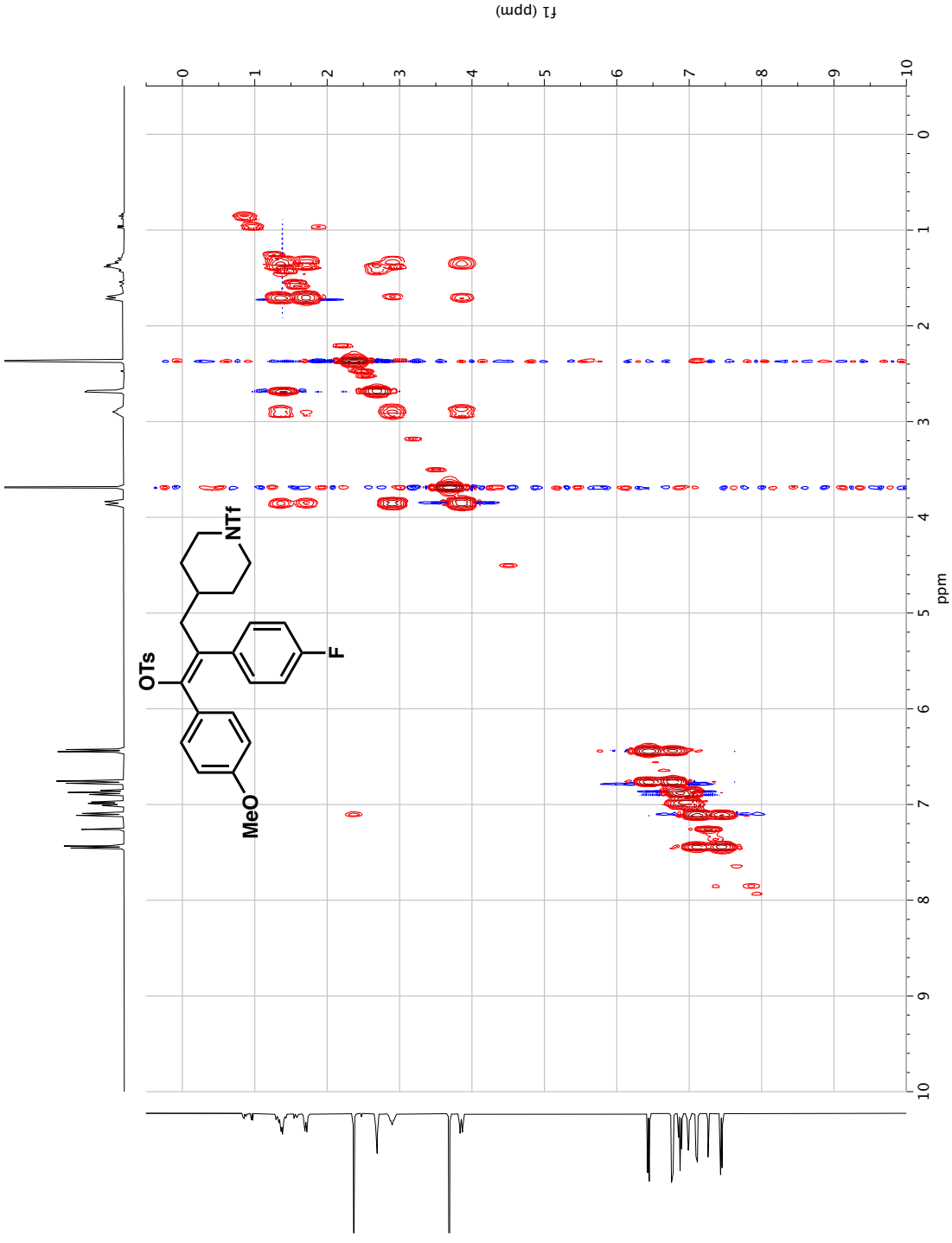
^{1}H NMR (400 MHz, $CDCl_3$) of **212e**.



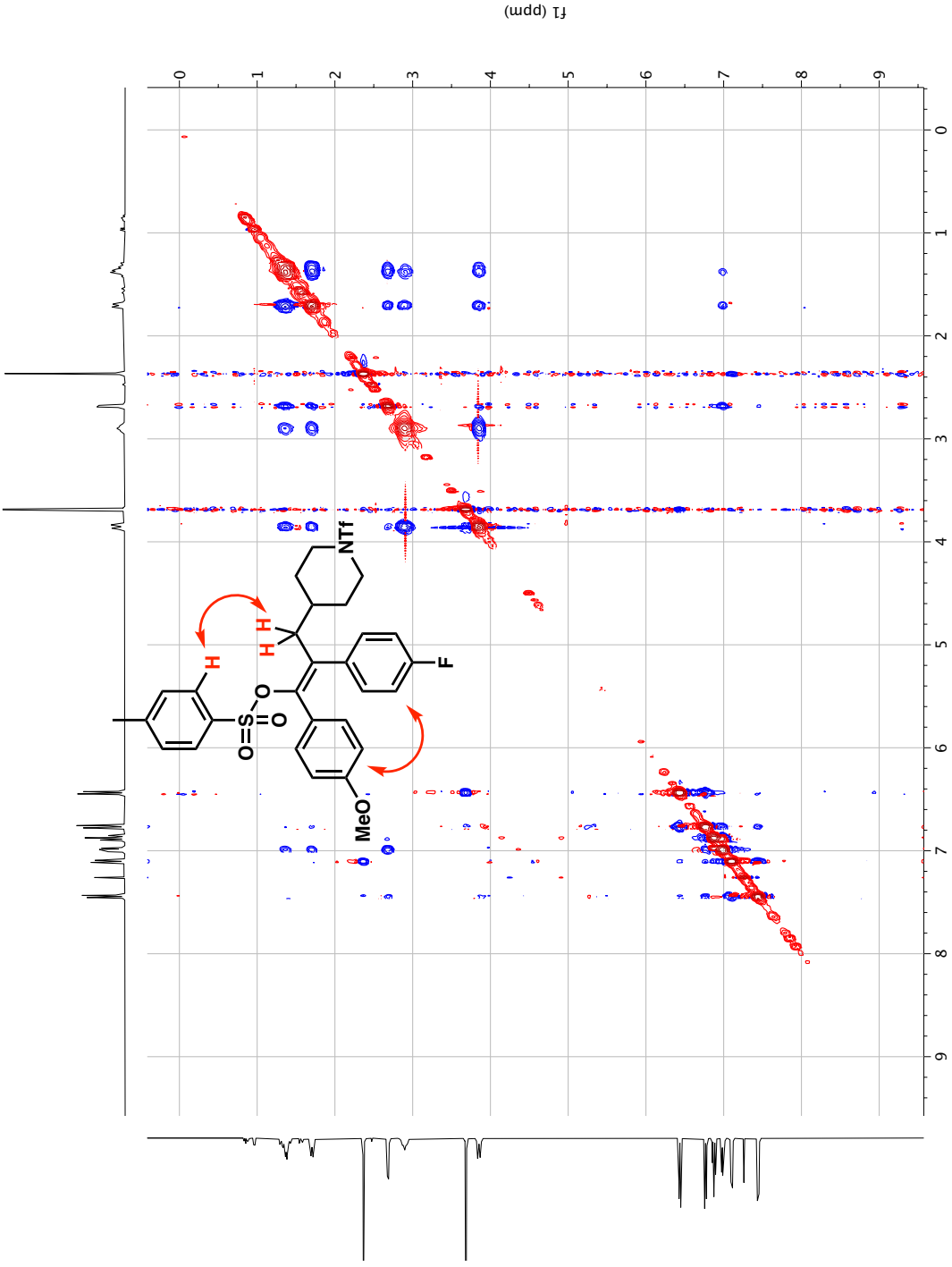
^{13}C NMR (101 MHz, $CDCl_3$) of **212e**.



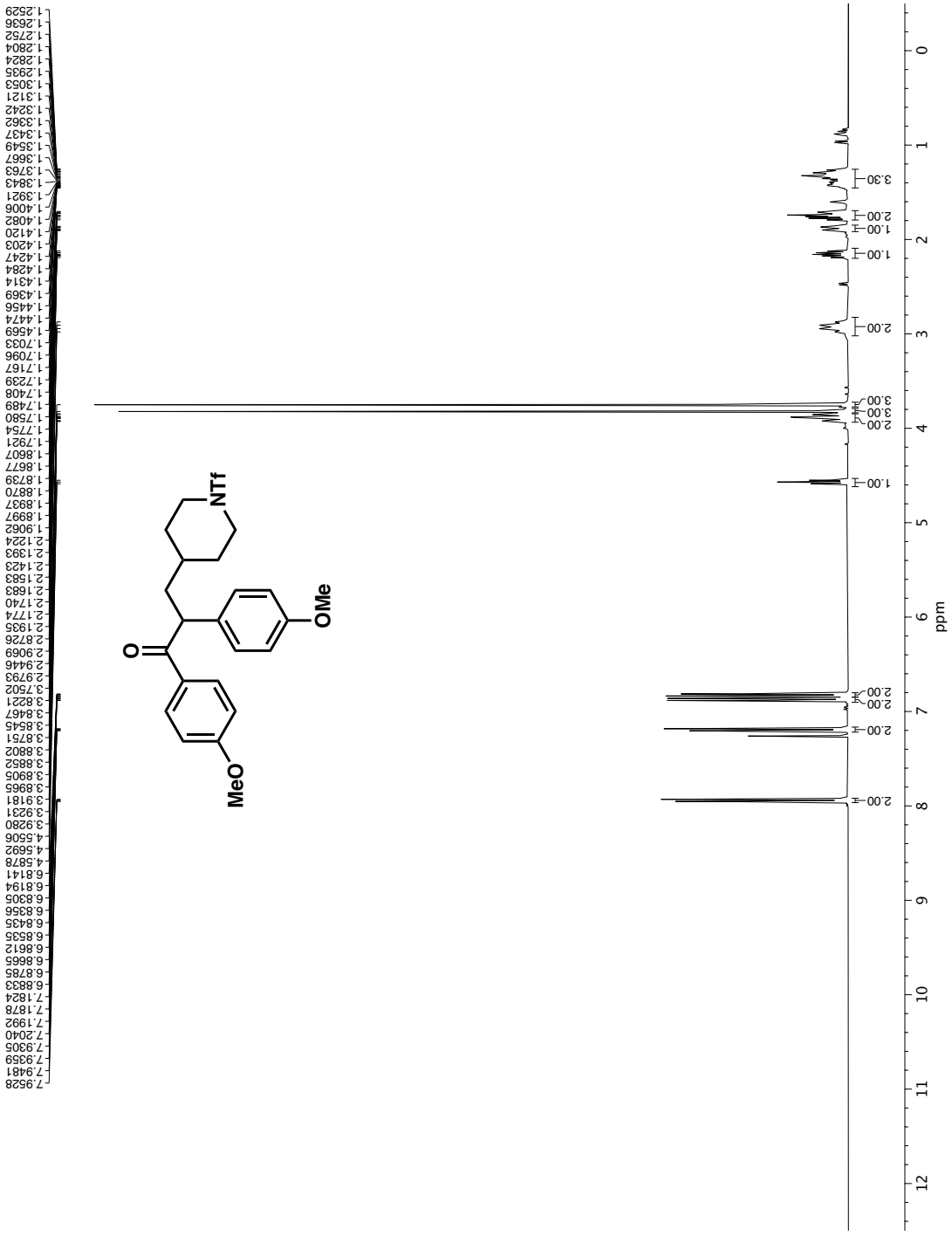
^{19}F NMR (376 MHz, $CDCl_3$) of **212e**.



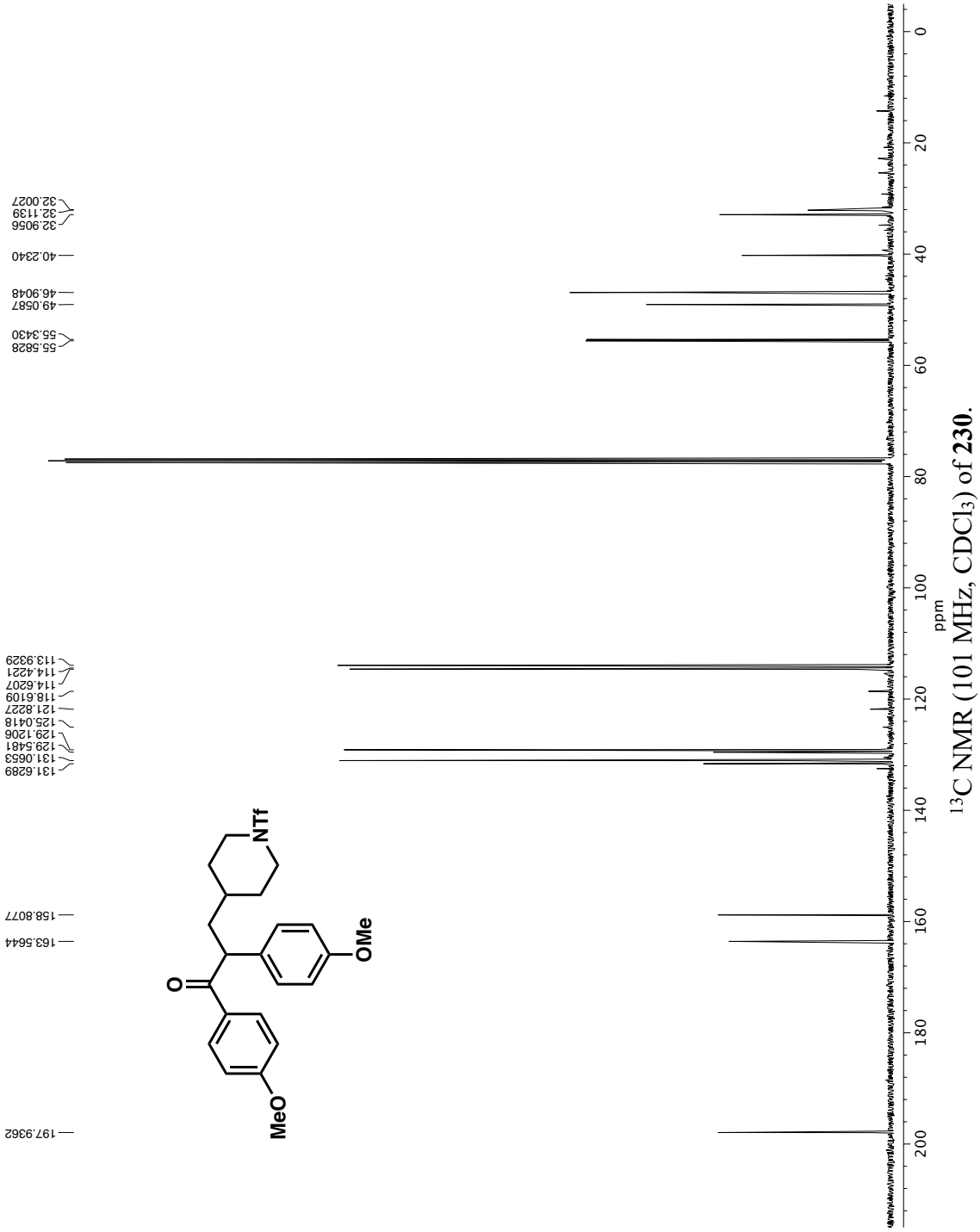
COSY NMR (400 MHz, $CDCl_3$) of **212e**.



NOESY NMR (400 MHz, $CDCl_3$) of **212e**.

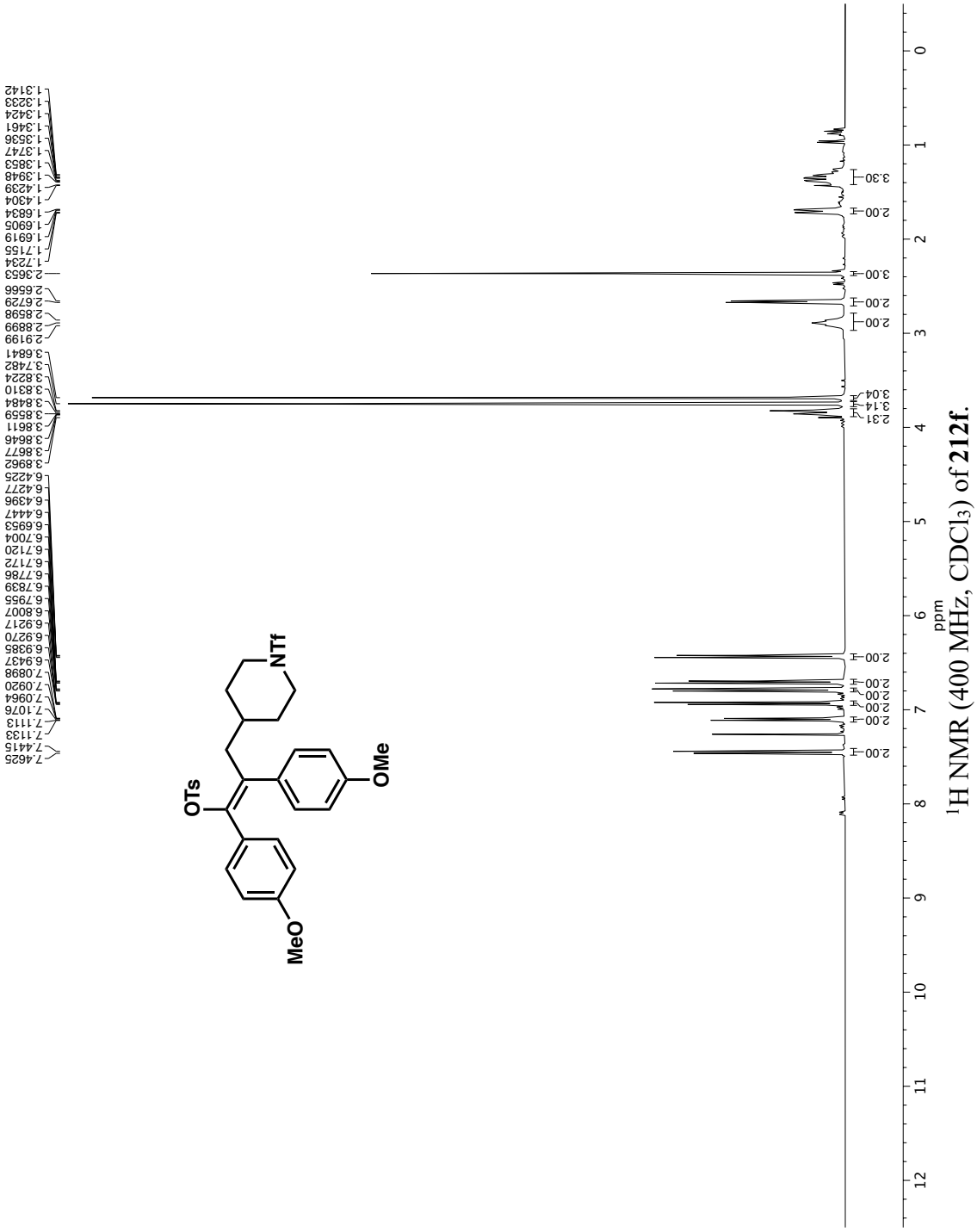


^{1}H NMR (400 MHz, $CDCl_3$) of **230**.

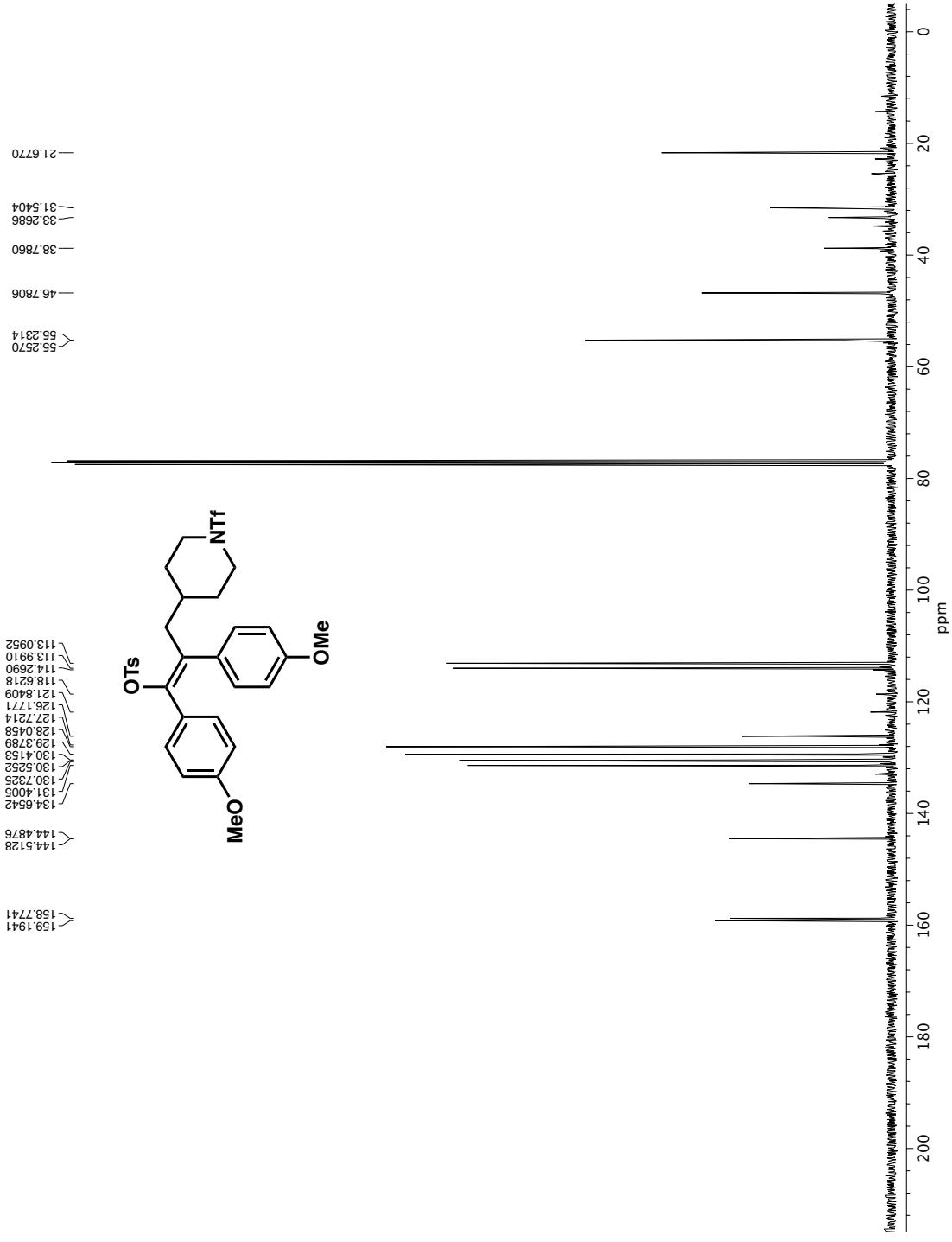


^{13}C NMR (101 MHz, $CDCl_3$) of **230**.

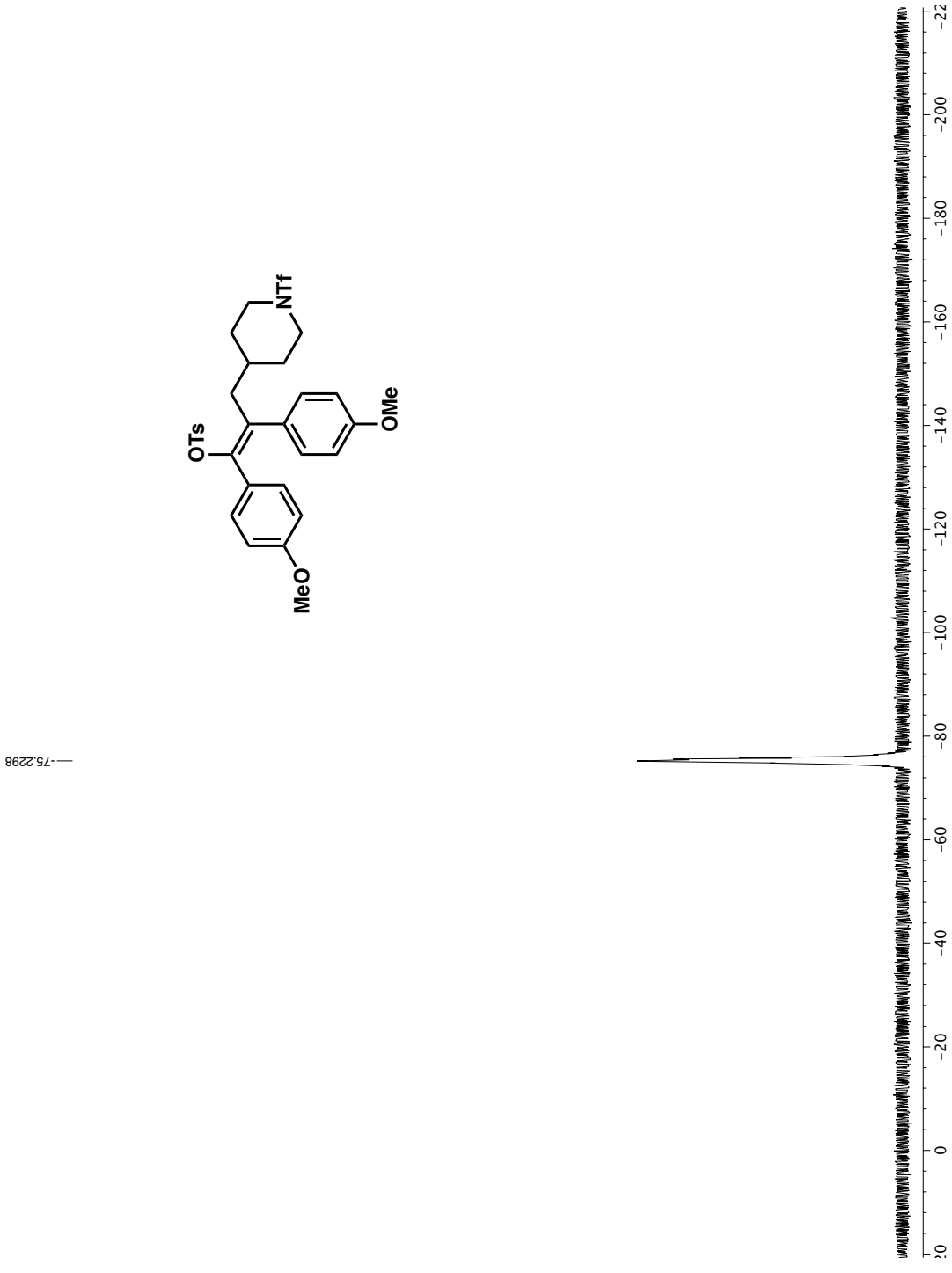
^{19}F NMR (376 MHz, $CDCl_3$) of **230**.



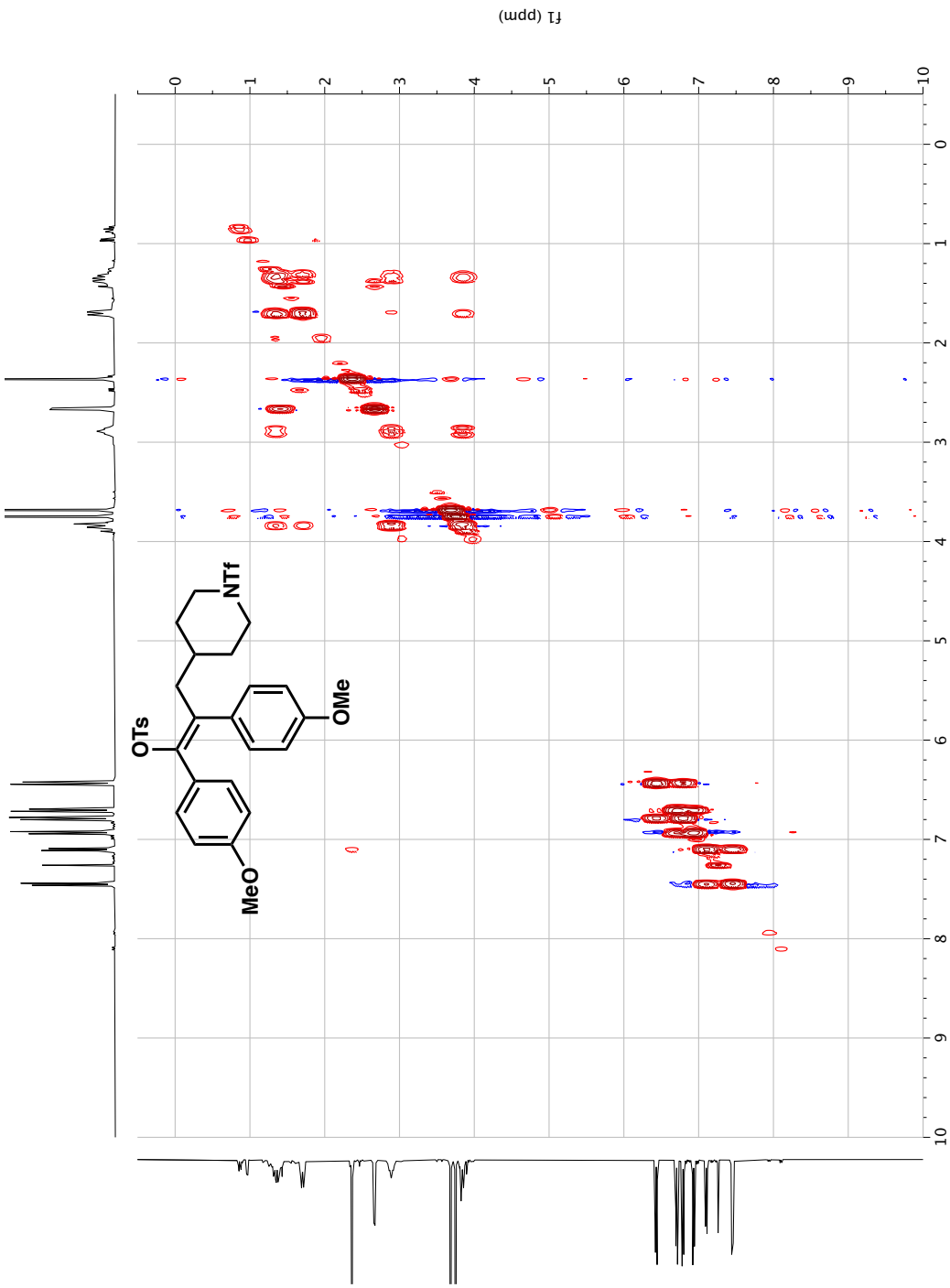
^{1}H NMR (400 MHz, $CDCl_3$) of **212f**.



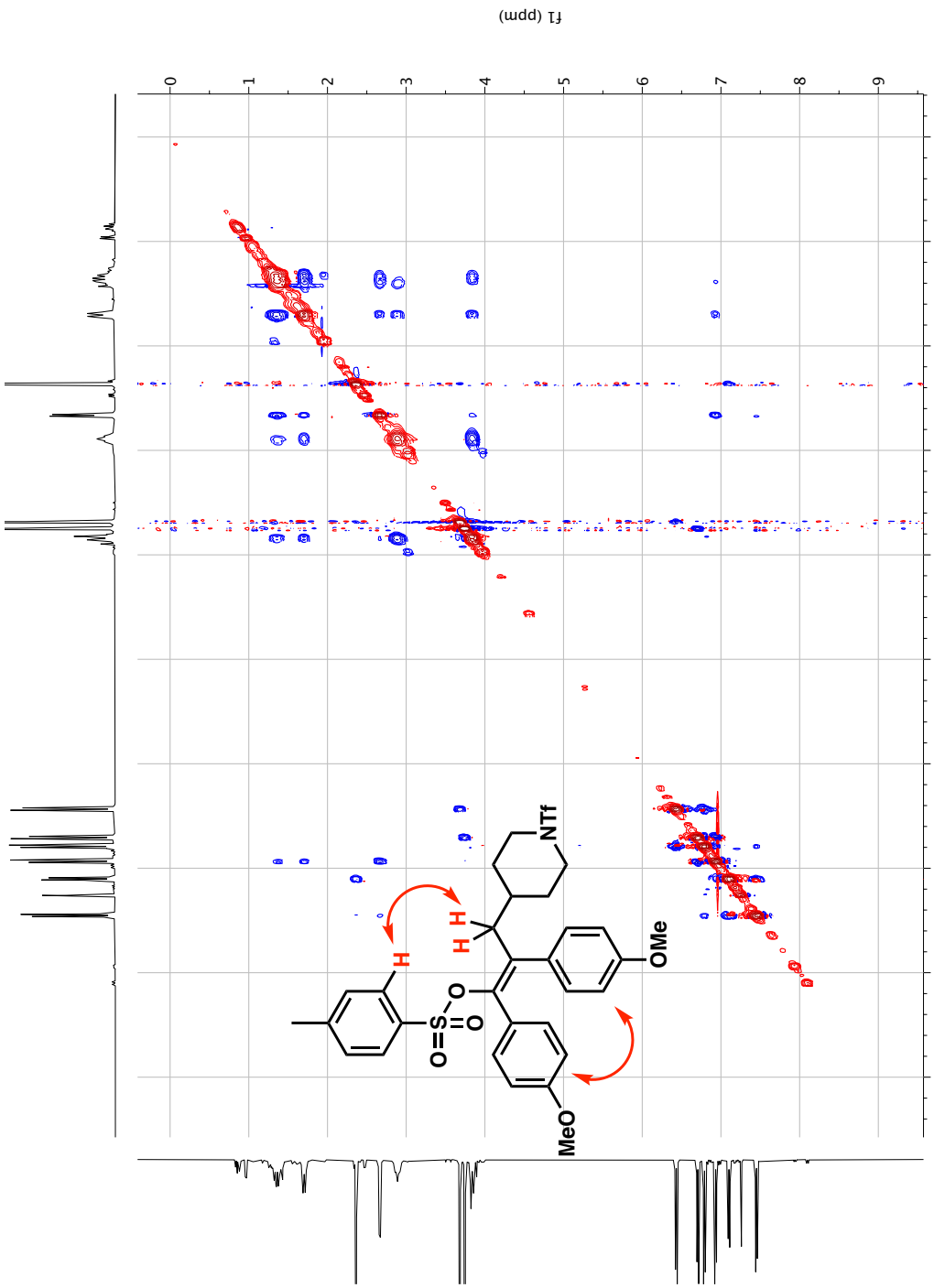
^{13}C NMR (101 MHz, $CDCl_3$) of **212f**.



^{19}F NMR (376 MHz, $CDCl_3$) of **212f**.

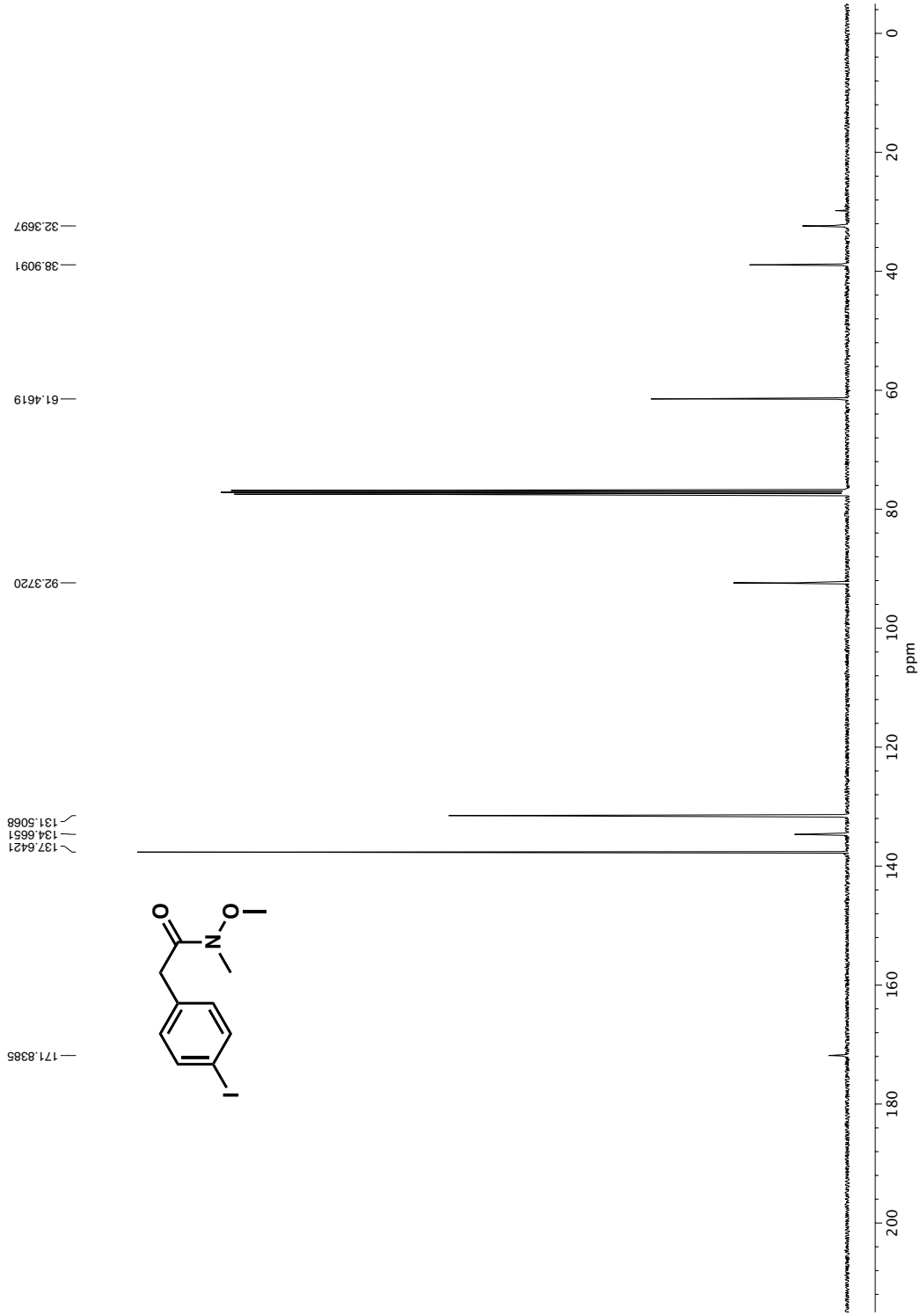


COSY NMR (400 MHz, $CDCl_3$) of **212f**.

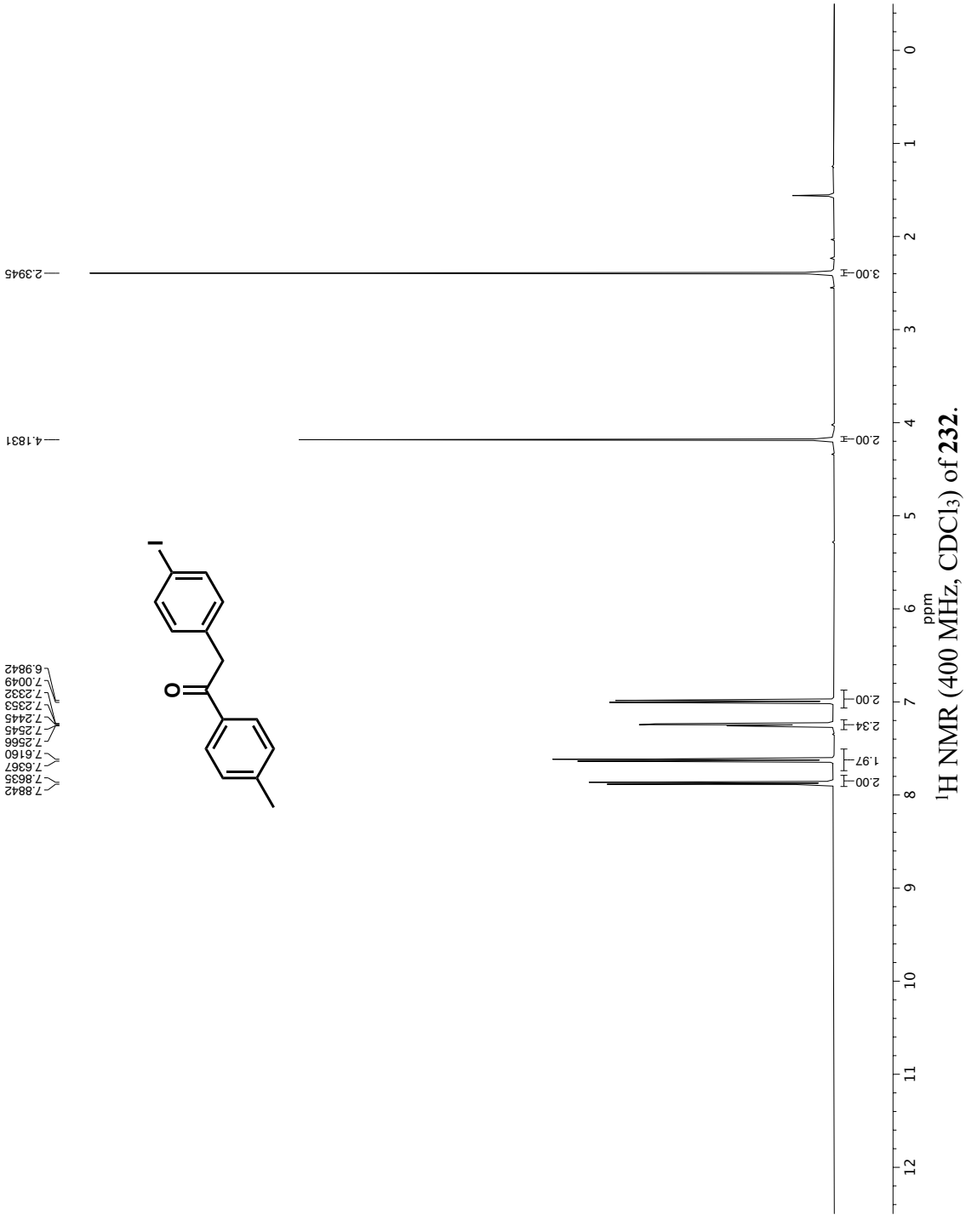


NOESY NMR (400 MHz, $CDCl_3$) of **212f**.

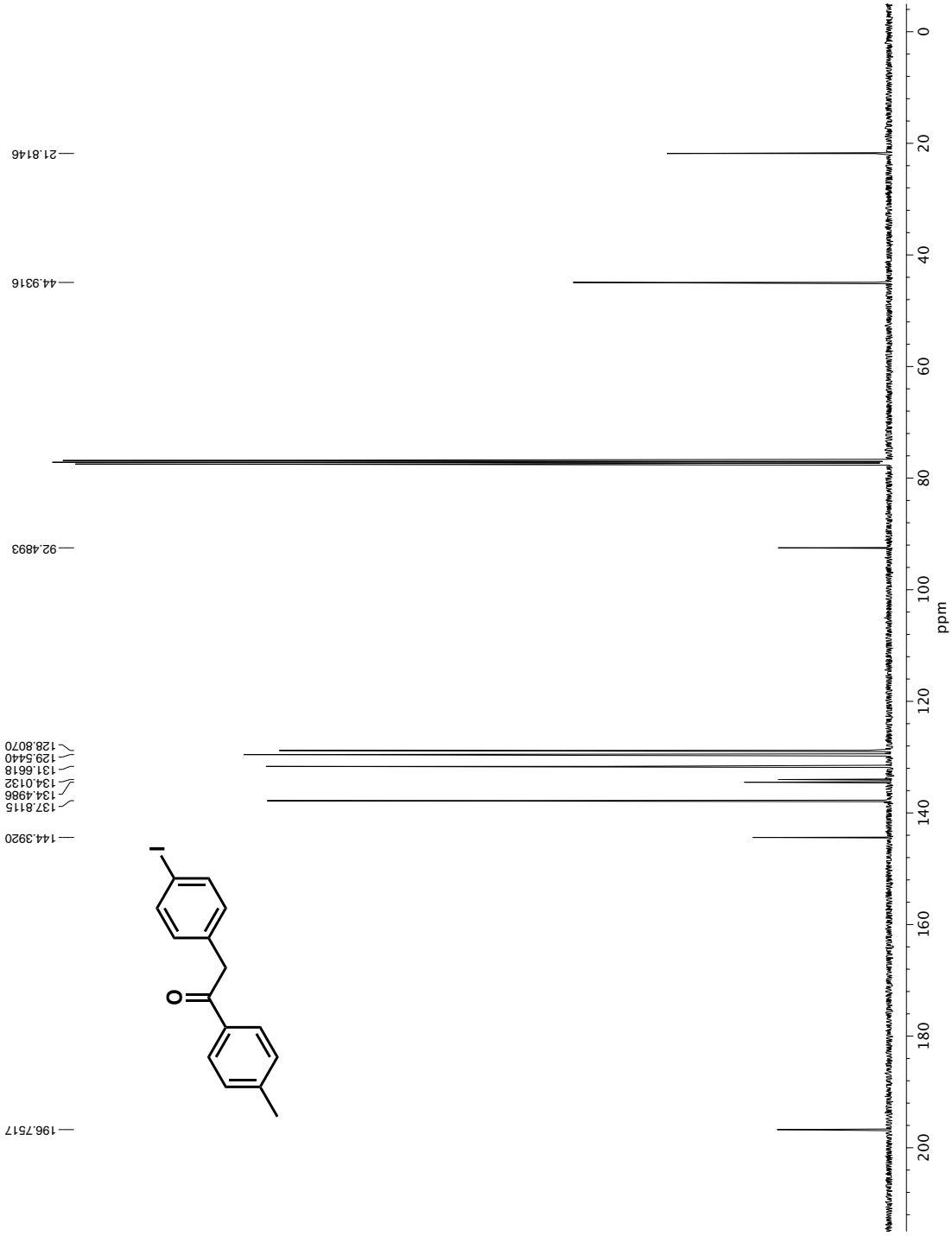
^{1}H NMR (400 MHz, $CDCl_3$) of **231**.



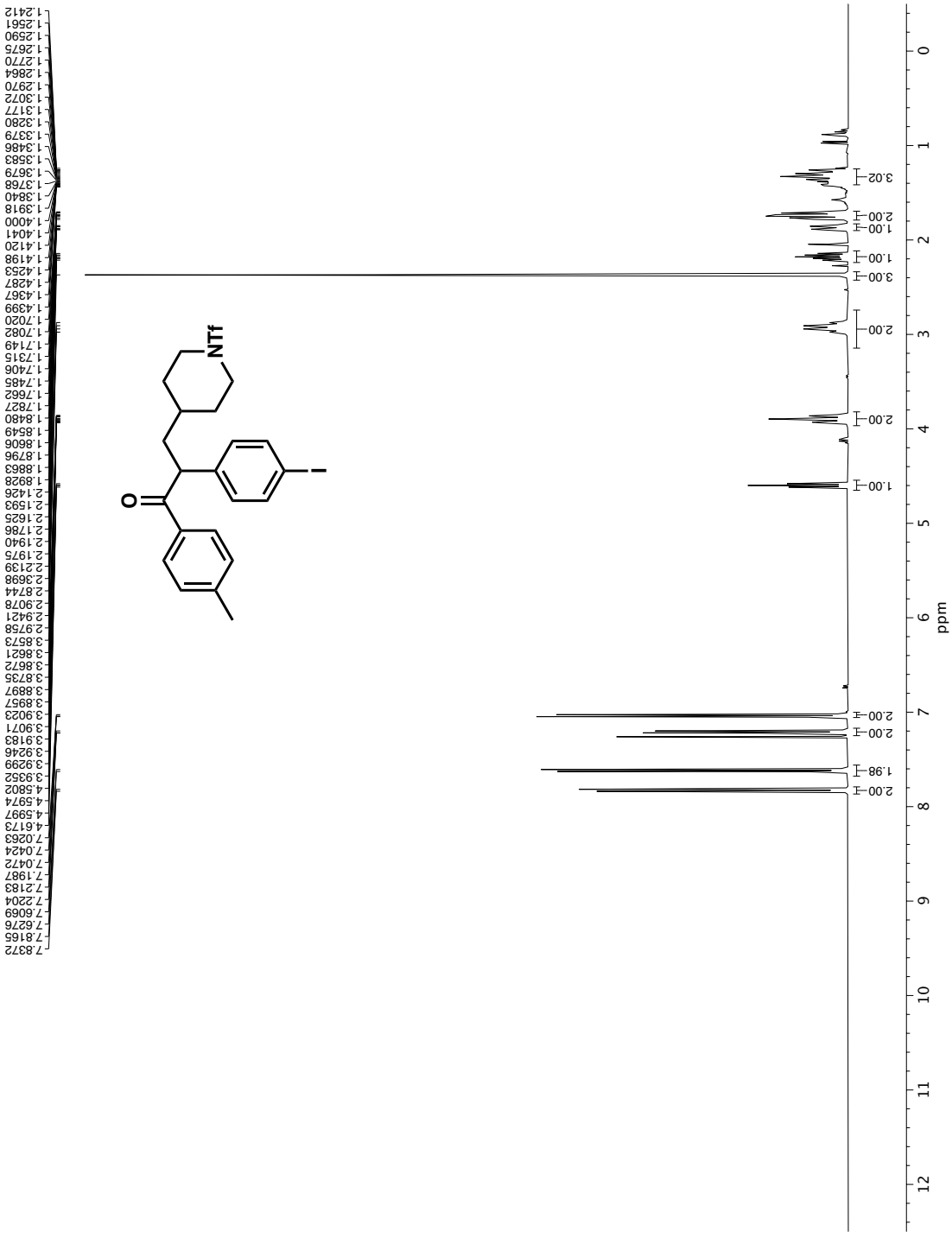
^{13}C NMR (101 MHz, $CDCl_3$) of **231**.



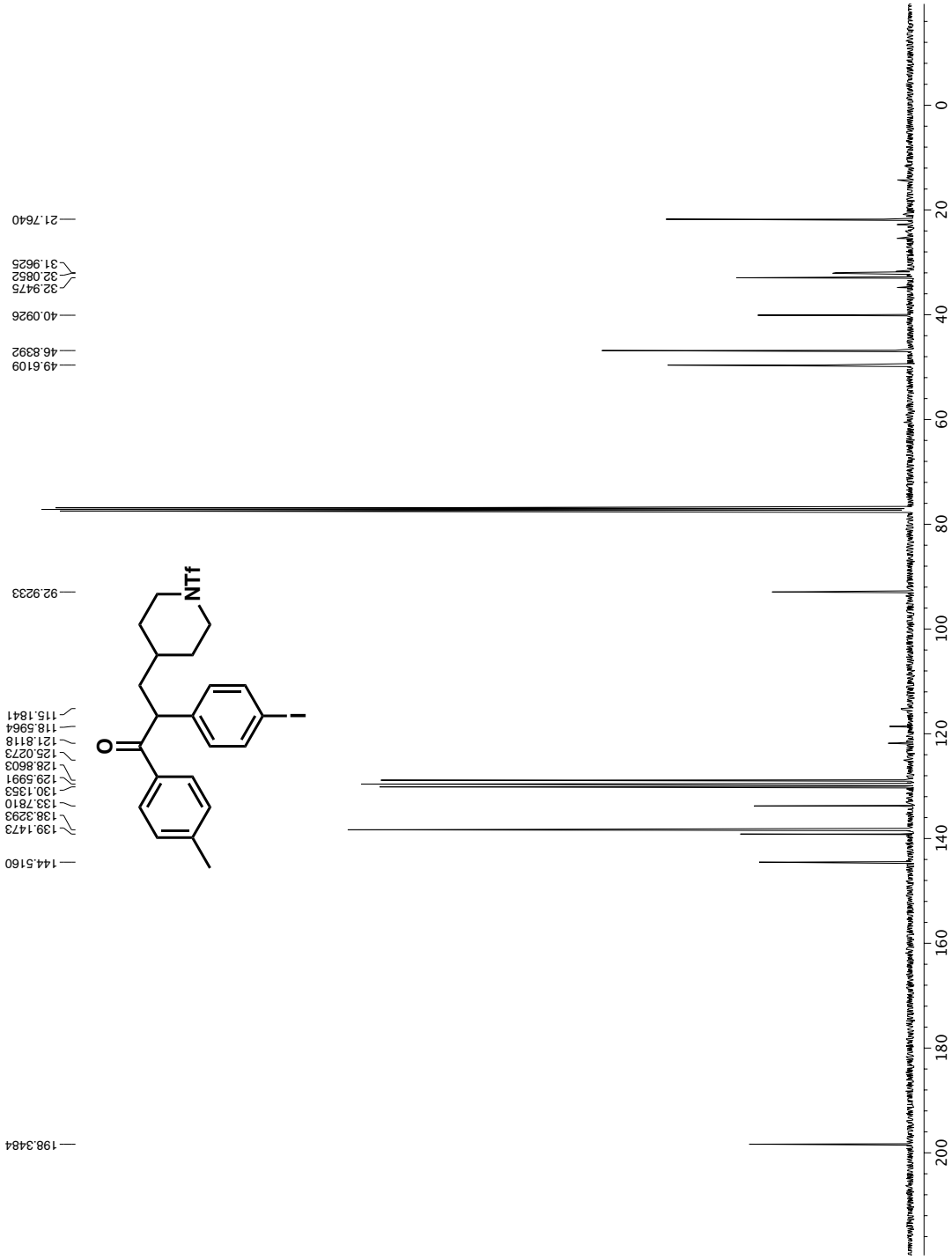
^{1}H NMR (400 MHz, $CDCl_3$) of **232**.



^{13}C NMR (101 MHz, $CDCl_3$) of **232**.

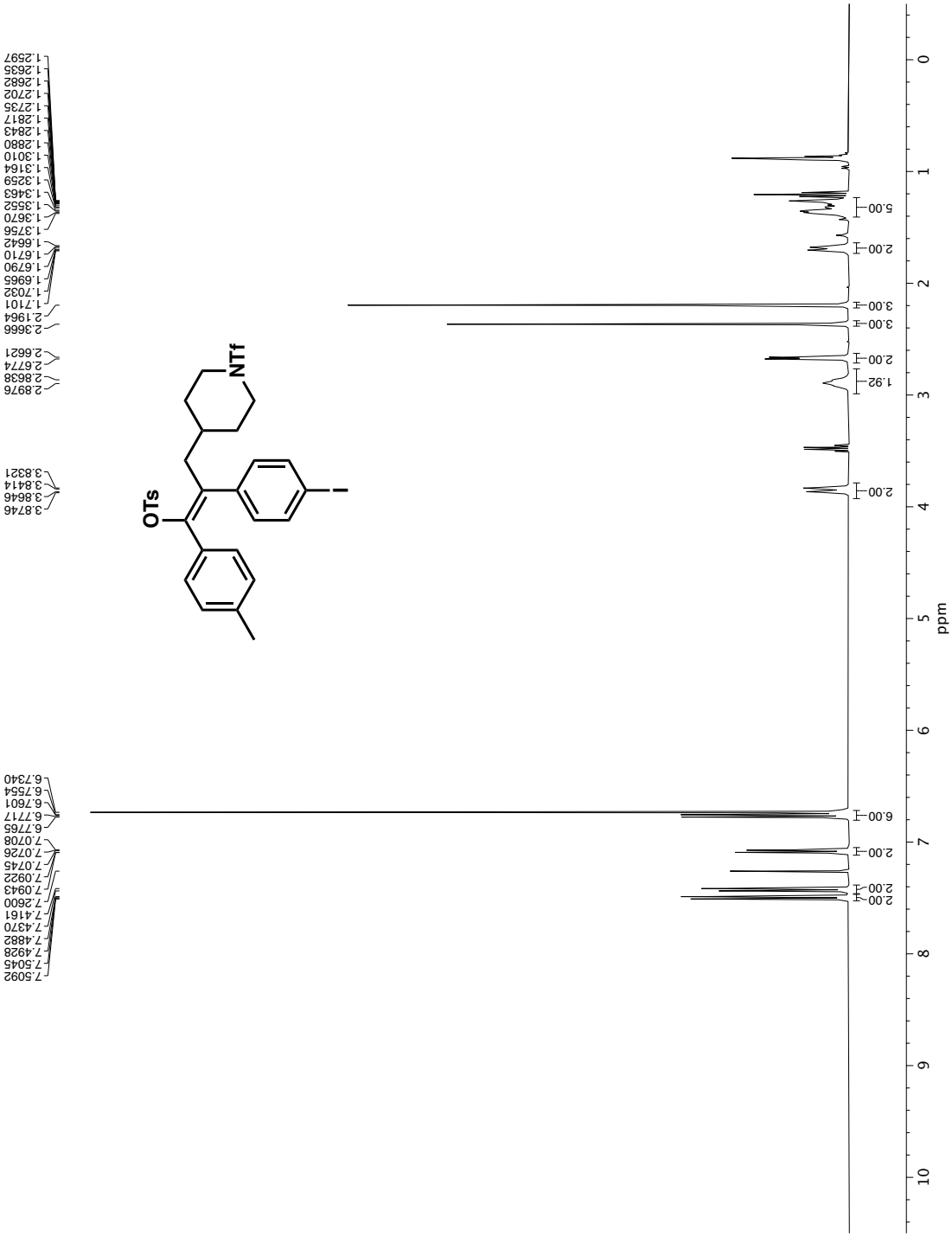


^{1}H NMR (400 MHz, $CDCl_3$) of **233**.

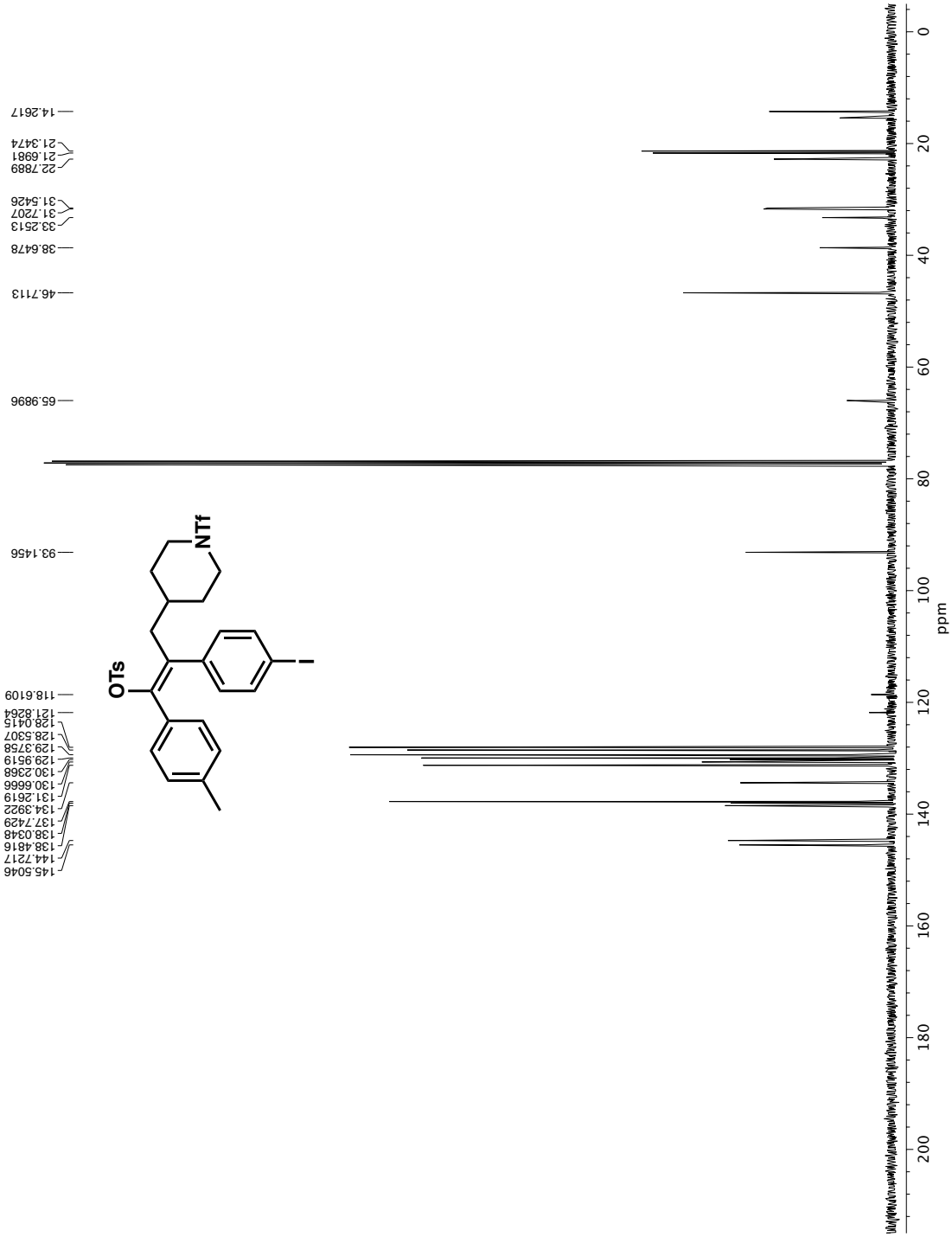


^{13}C NMR (101 MHz, $CDCl_3$) of **233**.

^{19}F NMR (376 MHz, $CDCl_3$) of **233**.

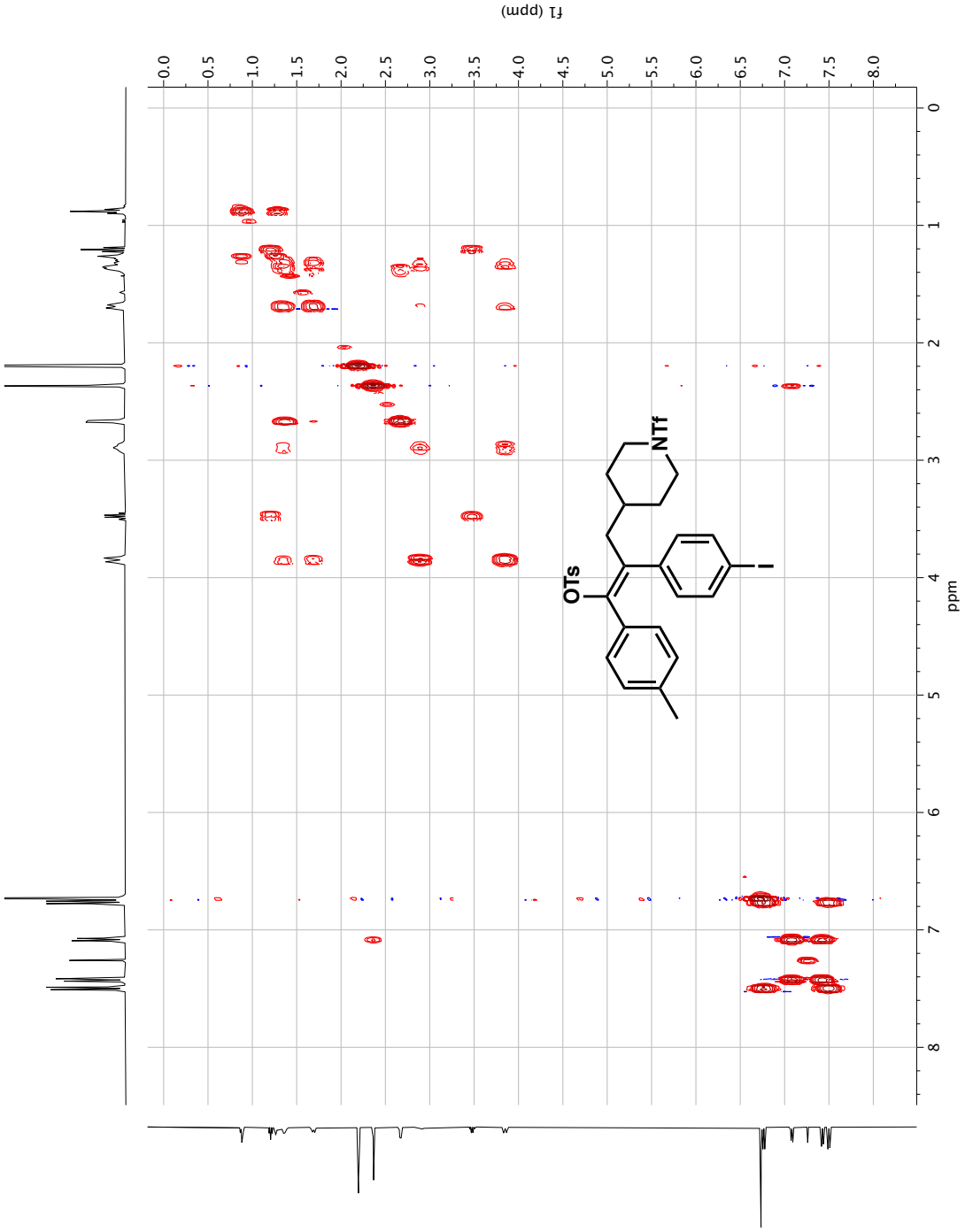


^{1}H NMR (400 MHz, $CDCl_3$) of **212g**.

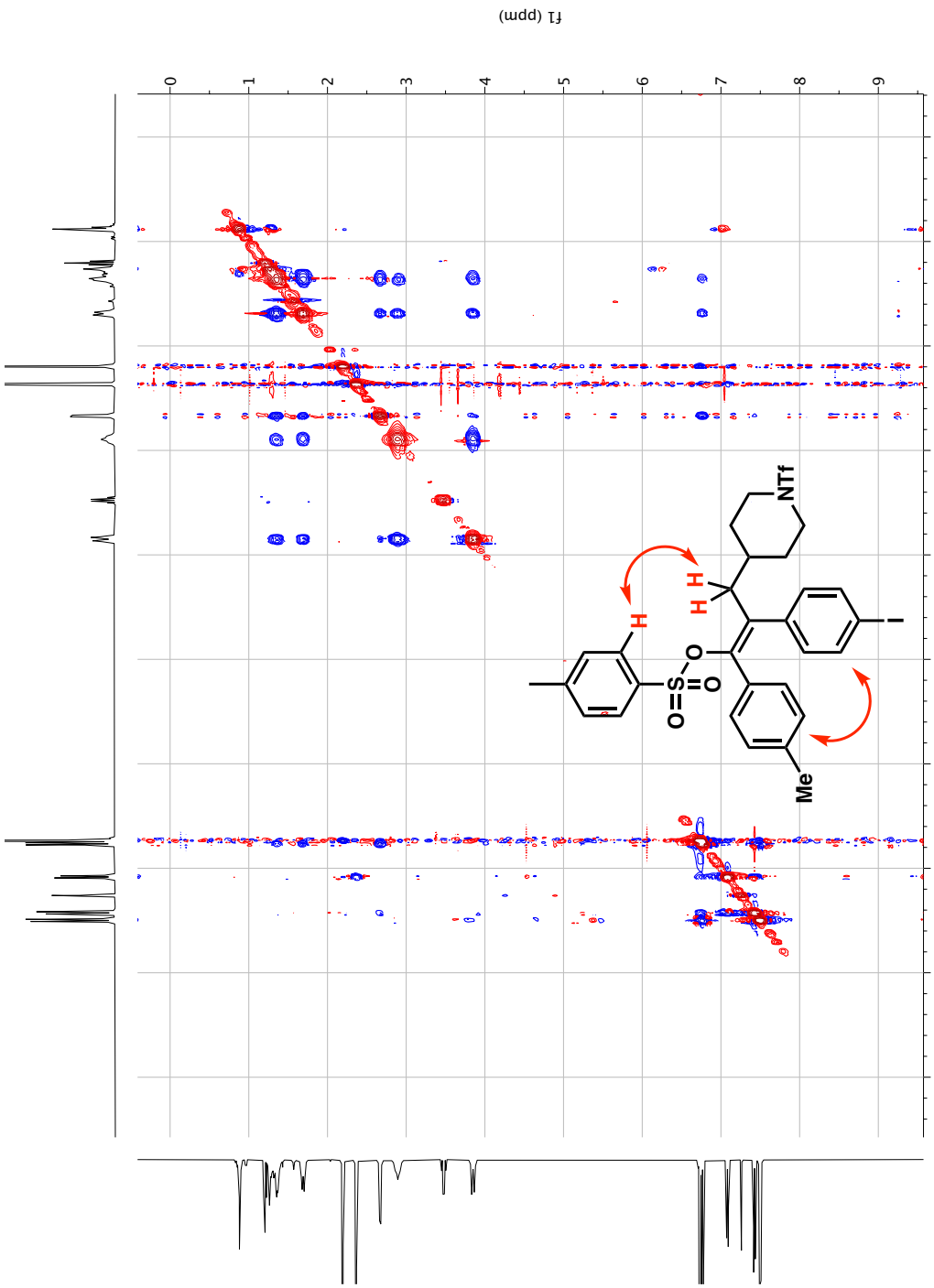


^{13}C NMR (101 MHz, $CDCl_3$) of **212g**.

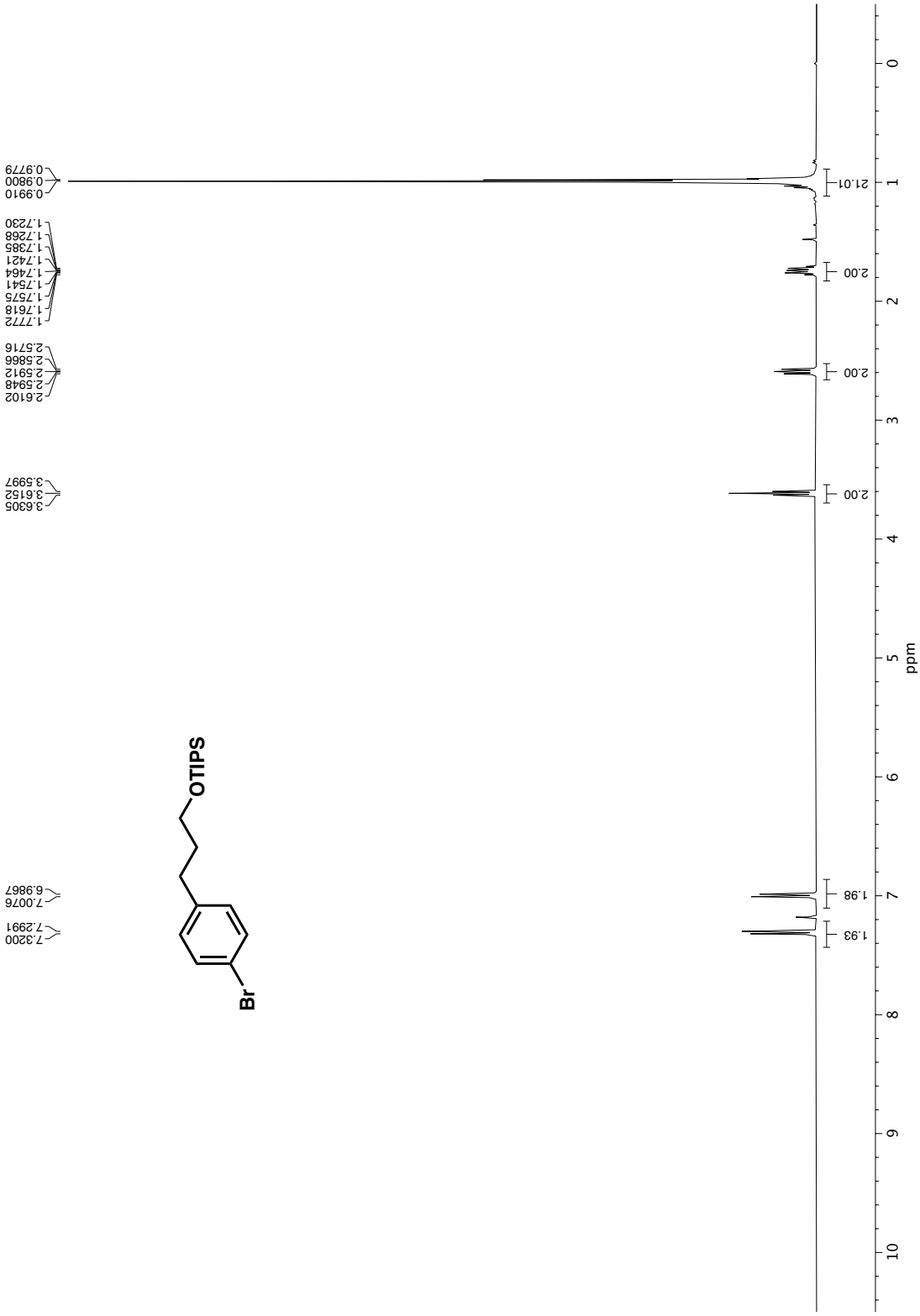
^{19}F NMR (376 MHz, $CDCl_3$) of **212g**.



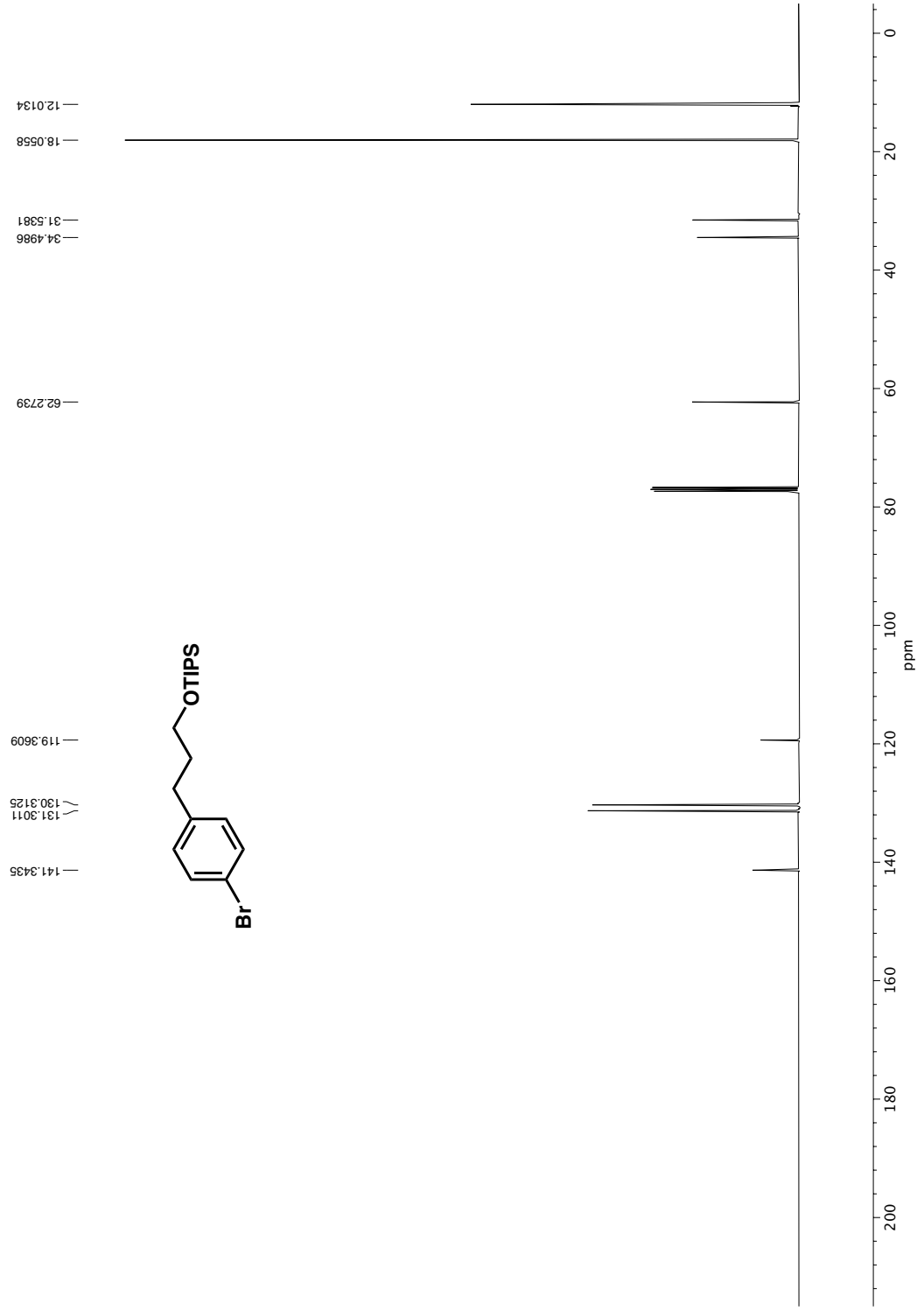
COSY NMR (400 MHz, $CDCl_3$) of **212g**.



NOESY NMR (400 MHz, $CDCl_3$) of **212g**.

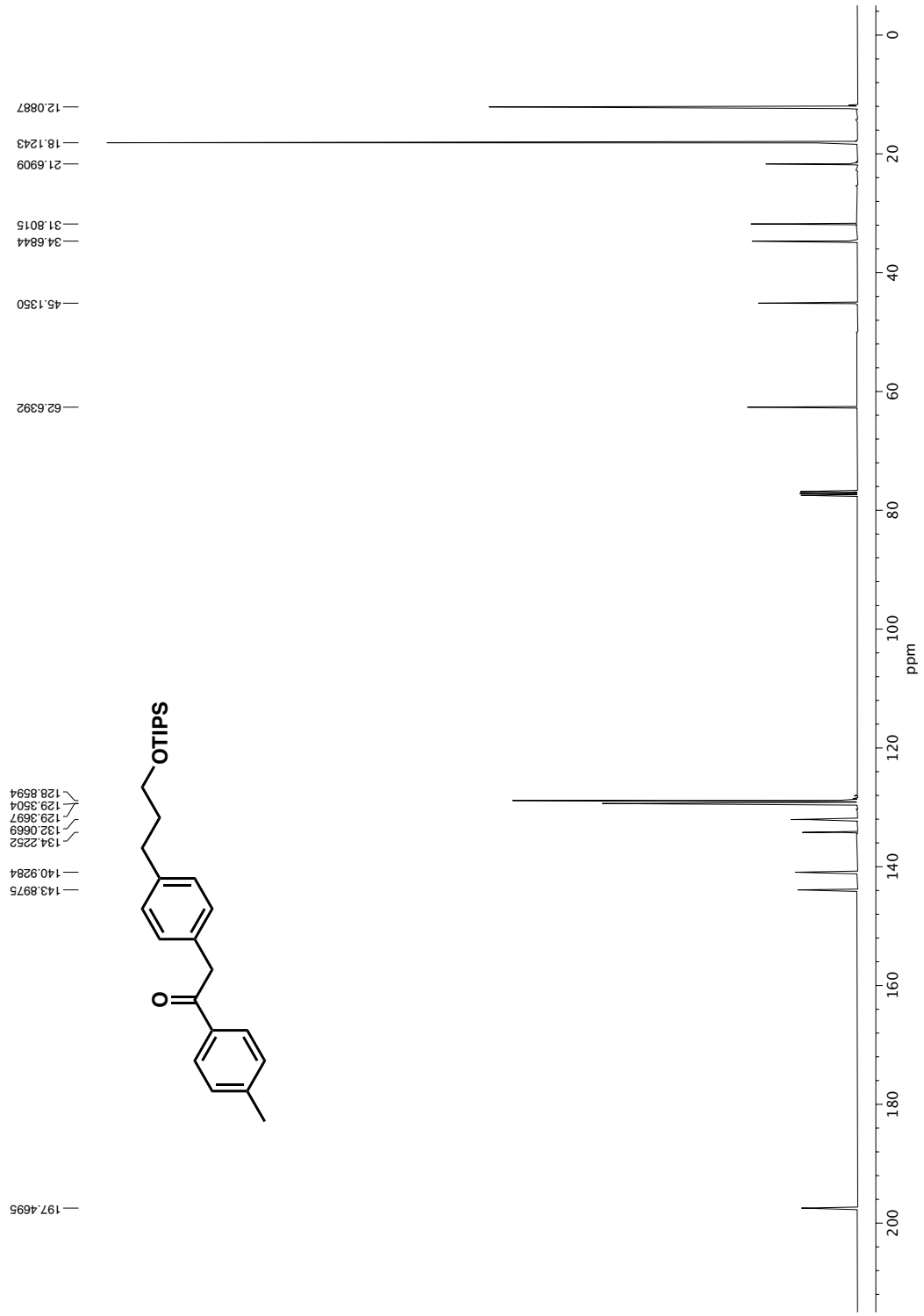


^{1}H NMR (400 MHz, $CDCl_3$) of **234**.



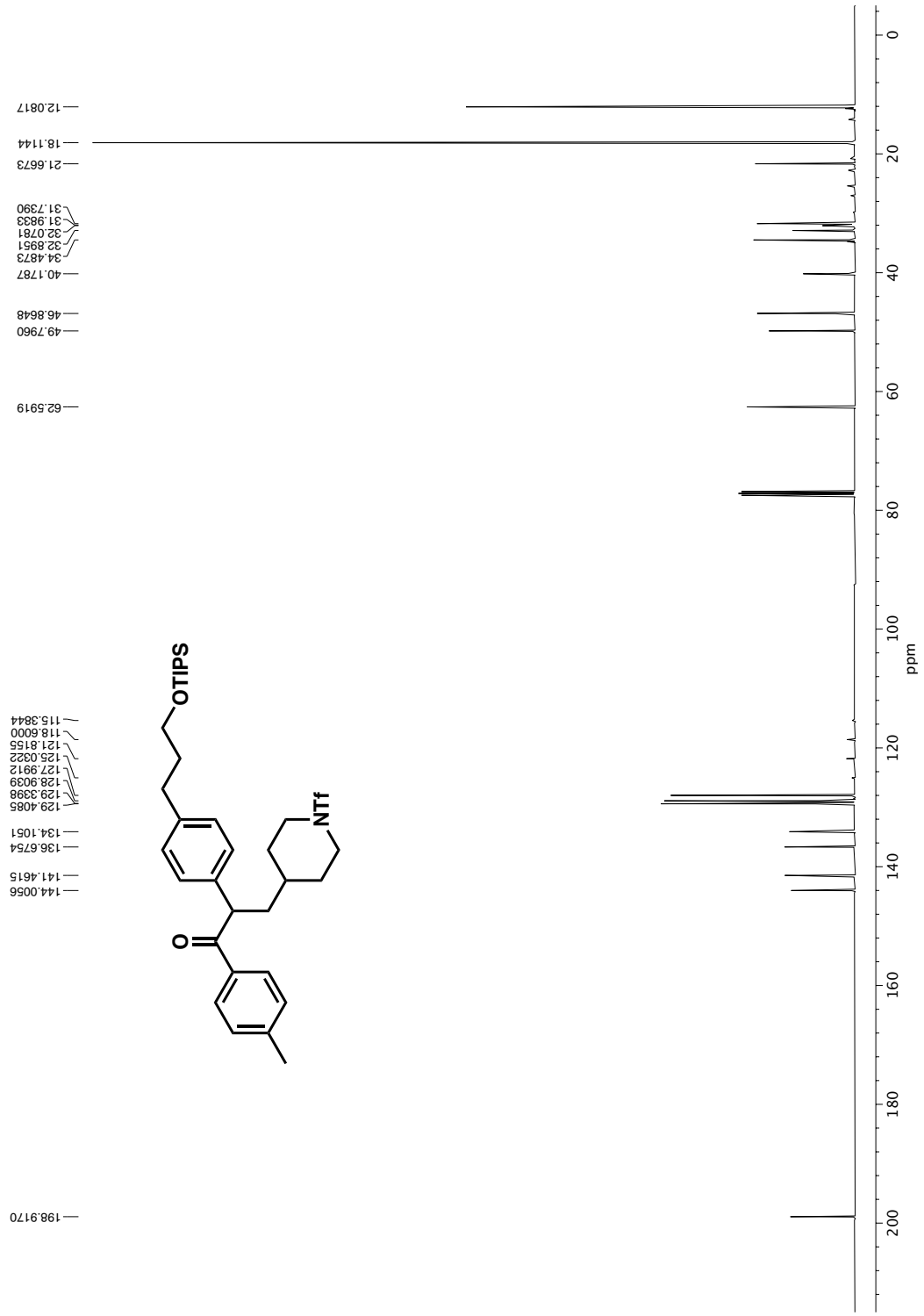
^{13}C NMR (101 MHz, $CDCl_3$) of **234**.

^{1}H NMR (400 MHz, $CDCl_3$) of **235**.



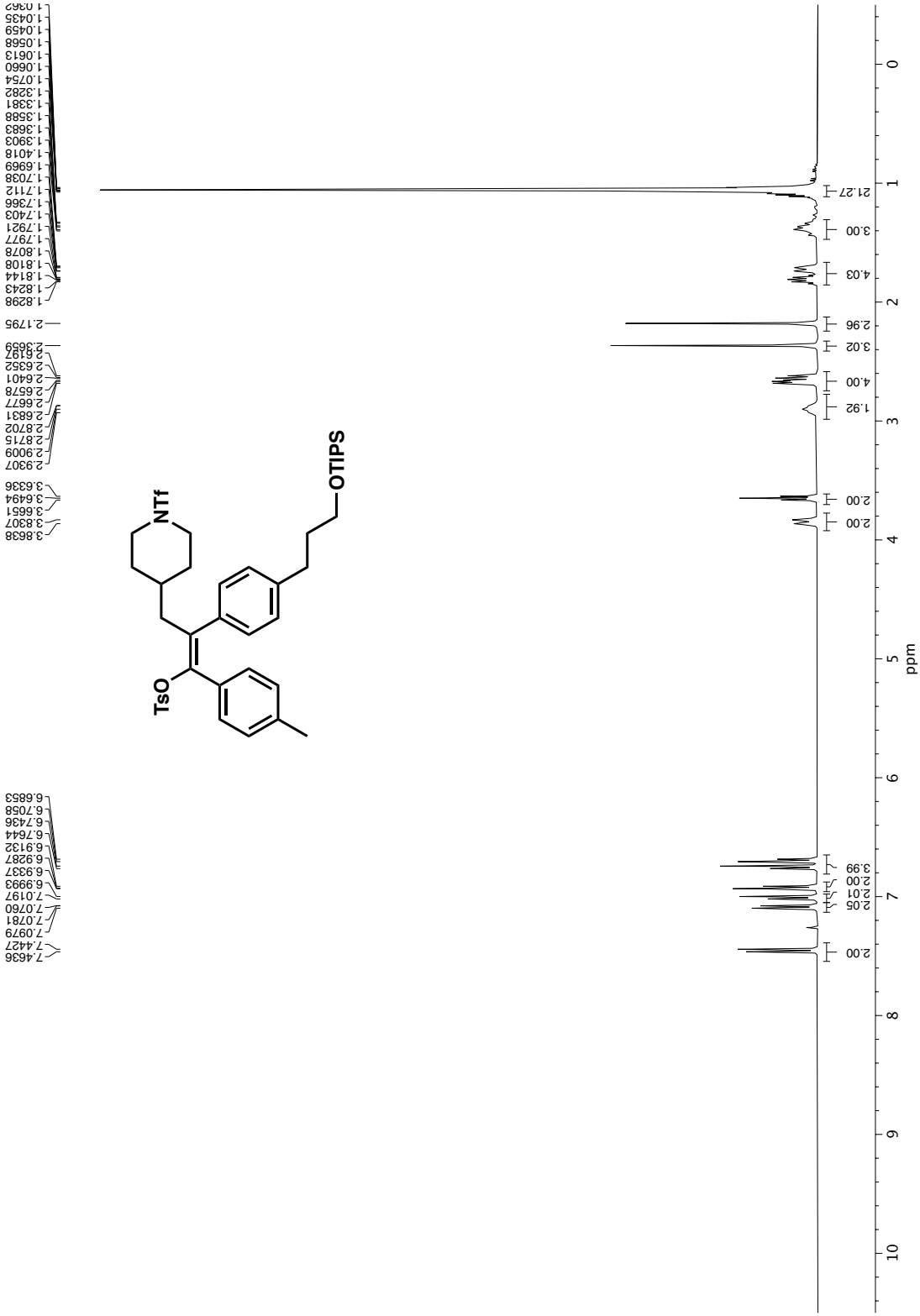
^{13}C NMR (101 MHz, $CDCl_3$) of **235**.

^{1}H NMR (400 MHz, $CDCl_3$) of **236**.

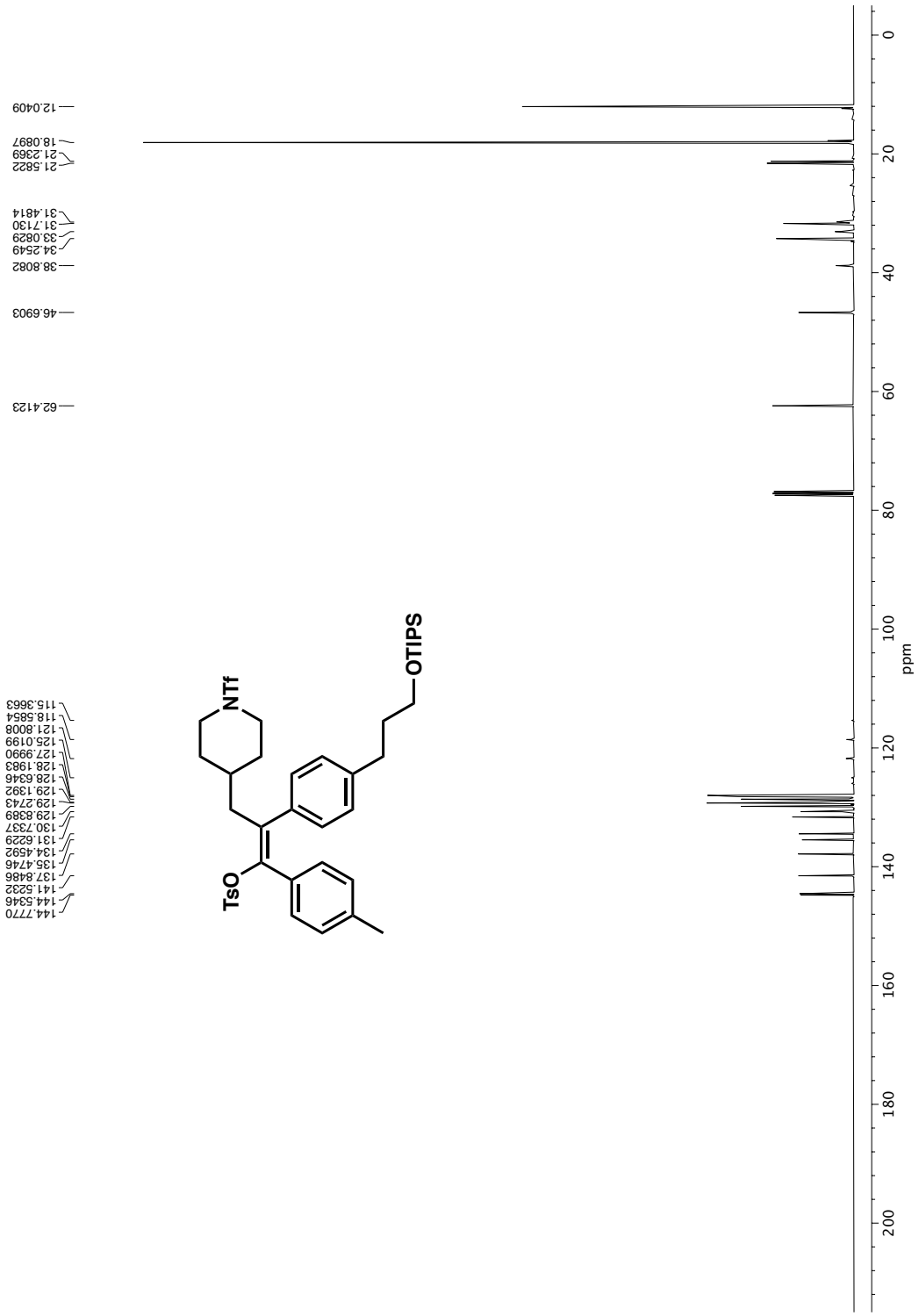


^{13}C NMR (101 MHz, $CDCl_3$) of **236**.

^{19}F NMR (376 MHz, $CDCl_3$) of **236**.

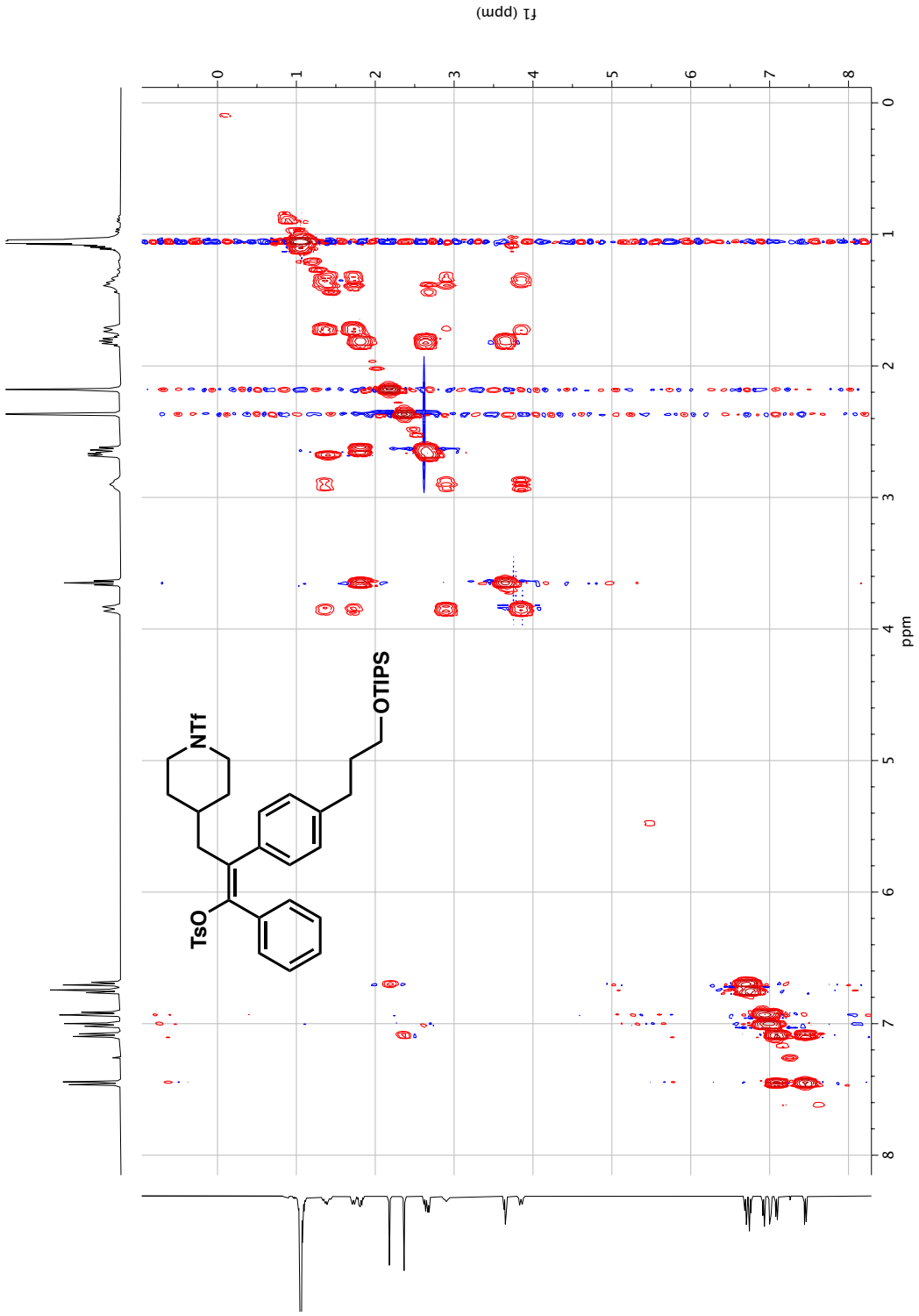


^{1}H NMR (400 MHz, $CDCl_3$) of **237**.

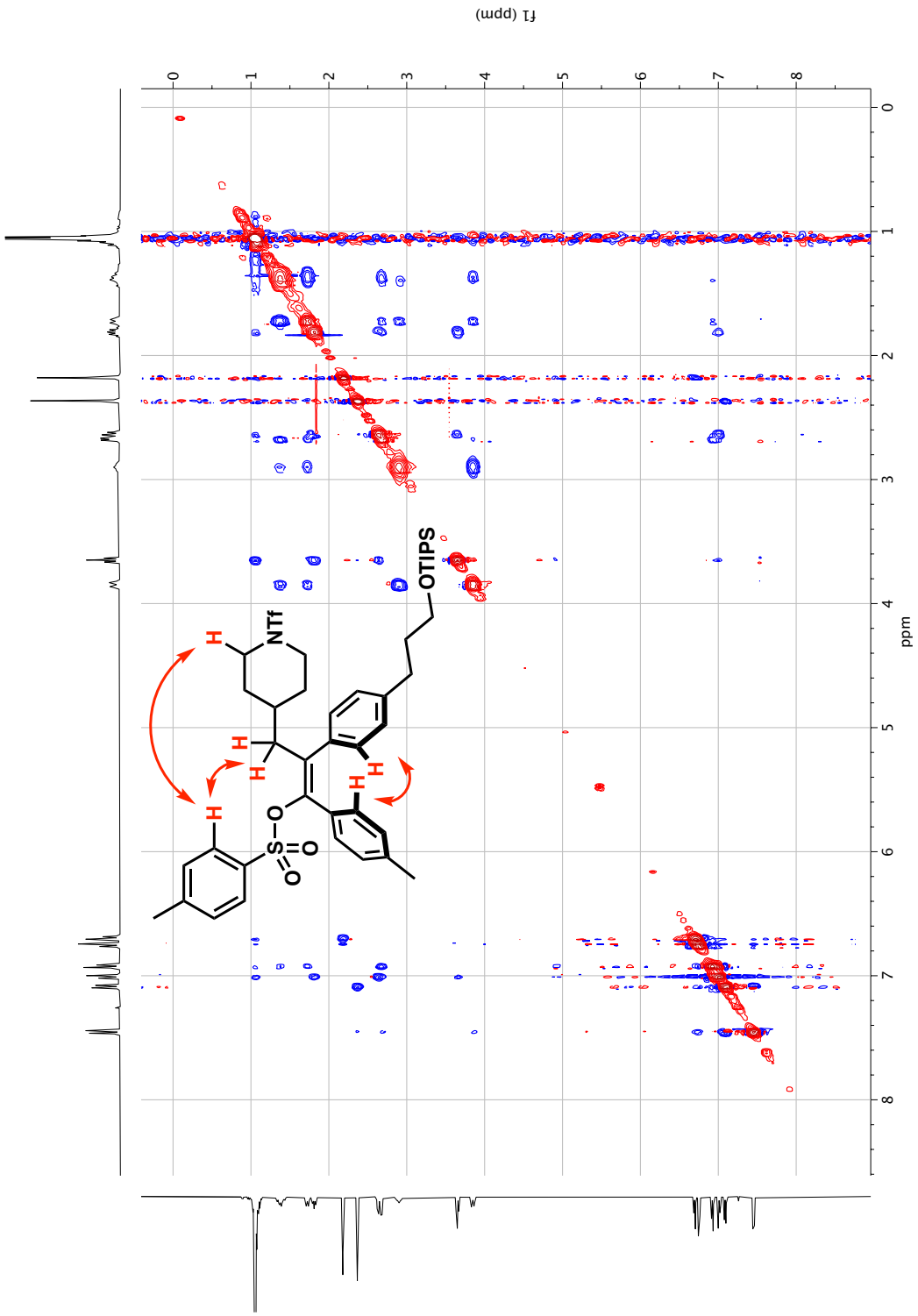


^{13}C NMR (101 MHz, $CDCl_3$) of **237**.

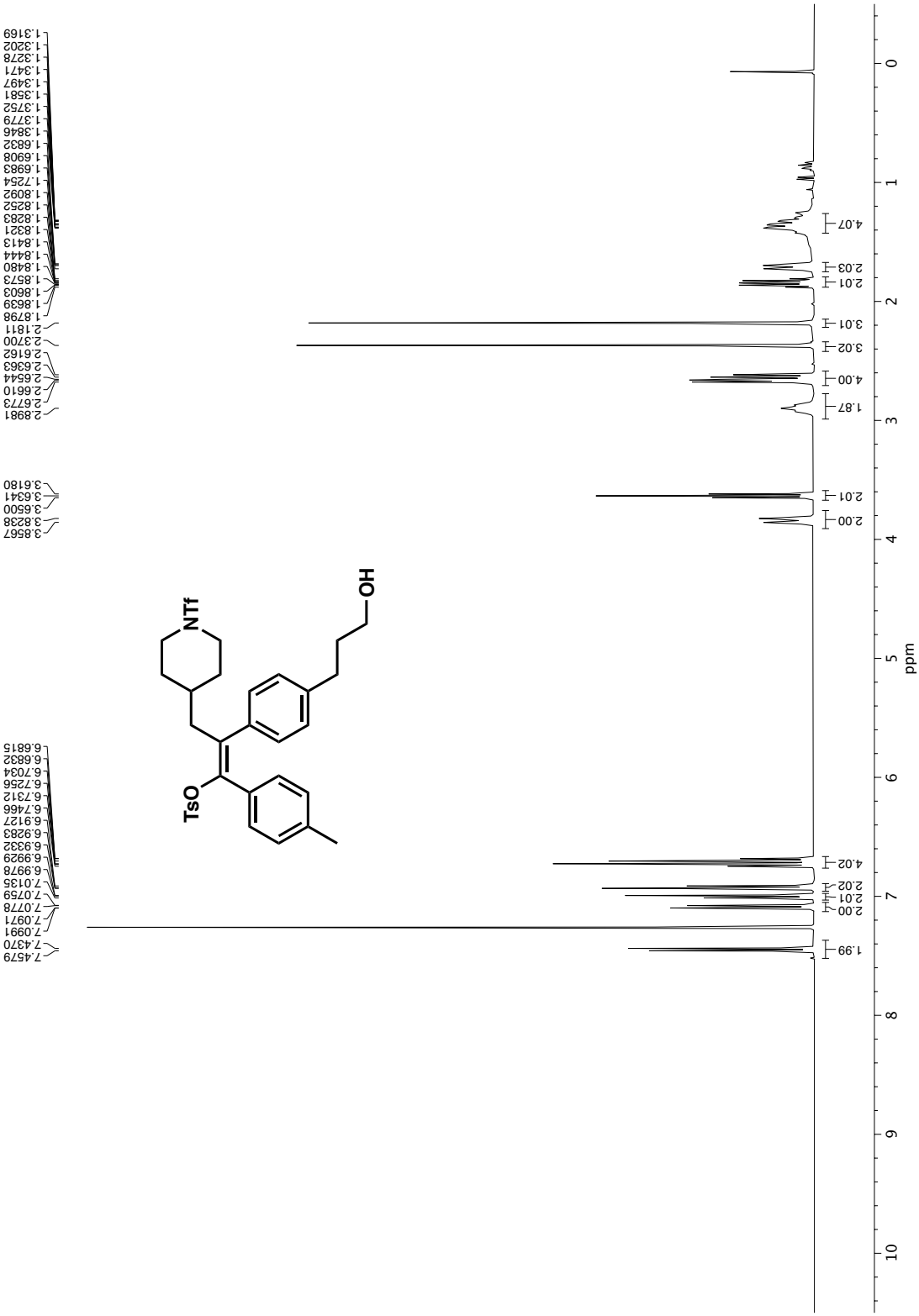
^{19}F NMR (376 MHz, $CDCl_3$) of **237**.



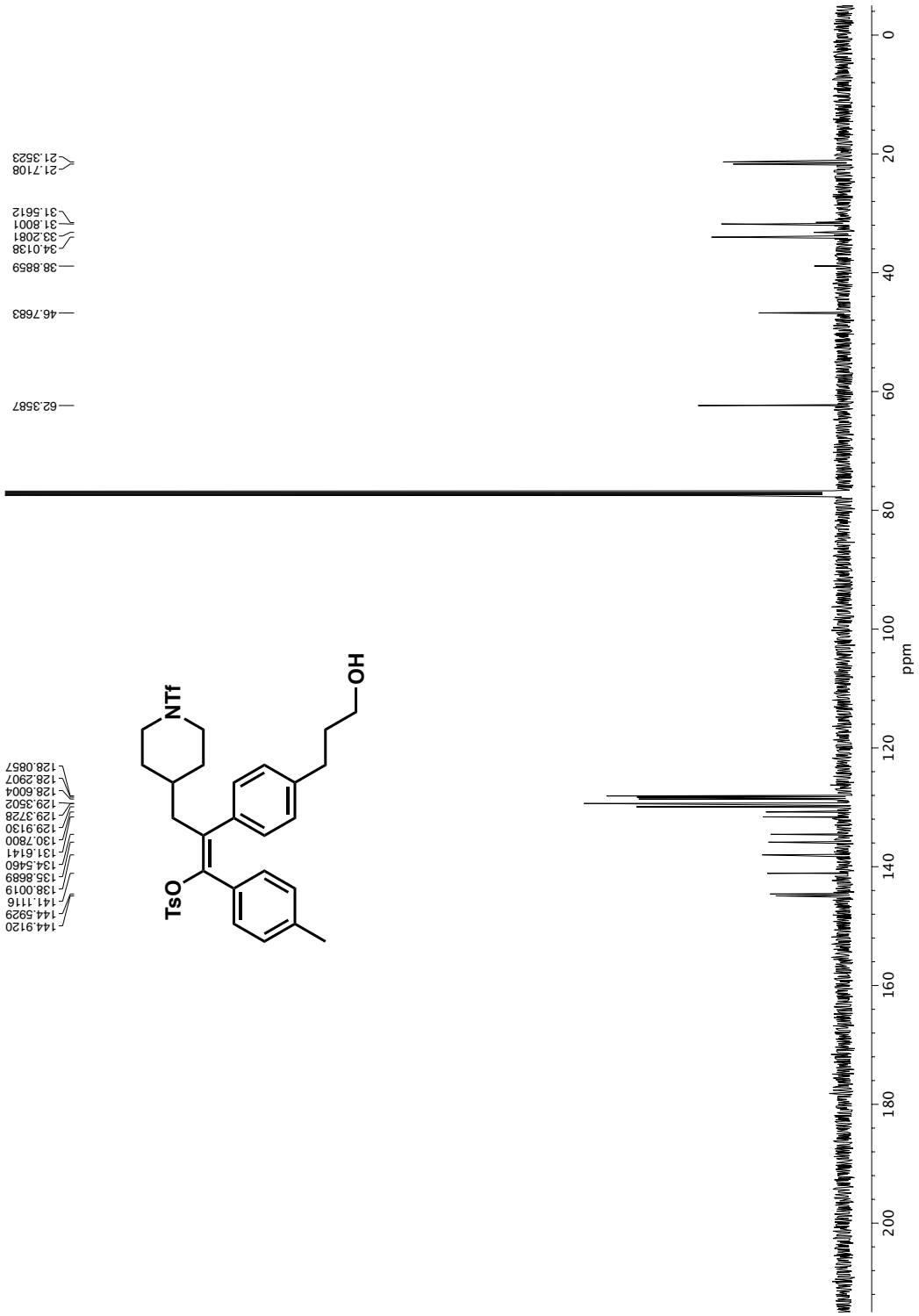
COSY NMR (400 MHz, $CDCl_3$) of **237**.



NOESY NMR (400 MHz, $CDCl_3$) of **237**.

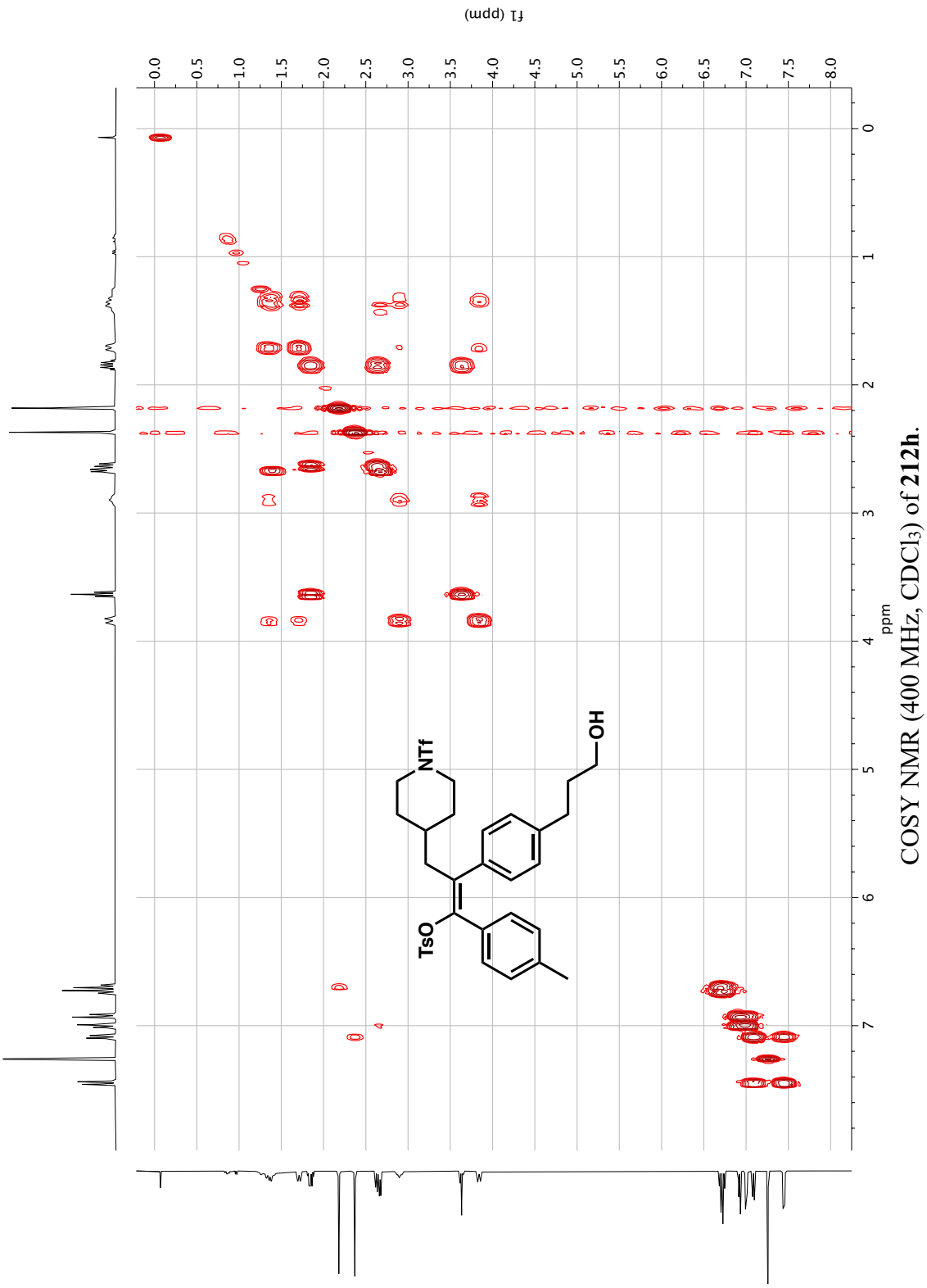


^{1}H NMR (400 MHz, $CDCl_3$) of **212h**.

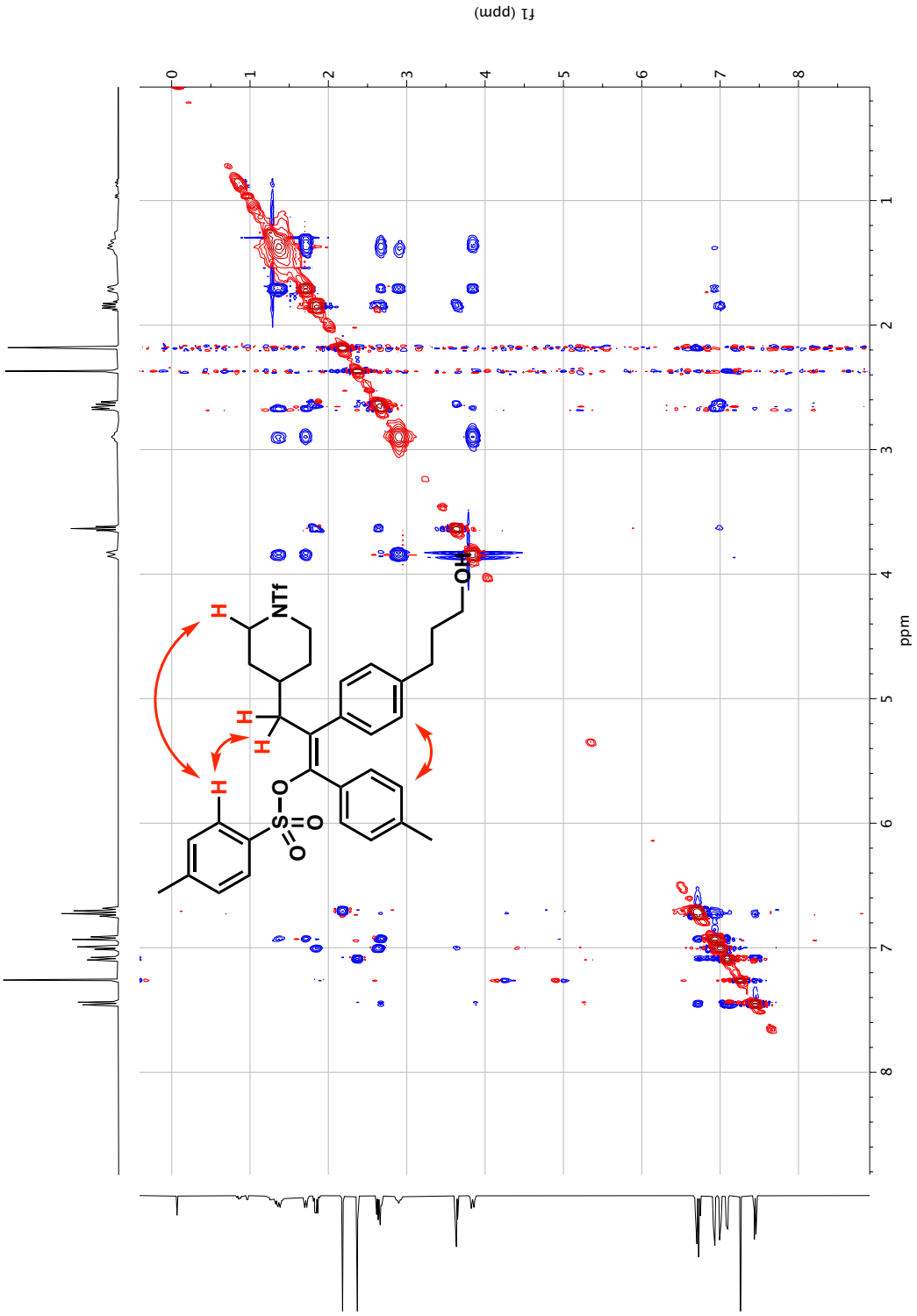


^{13}C NMR (101 MHz, $CDCl_3$) of **212h**.

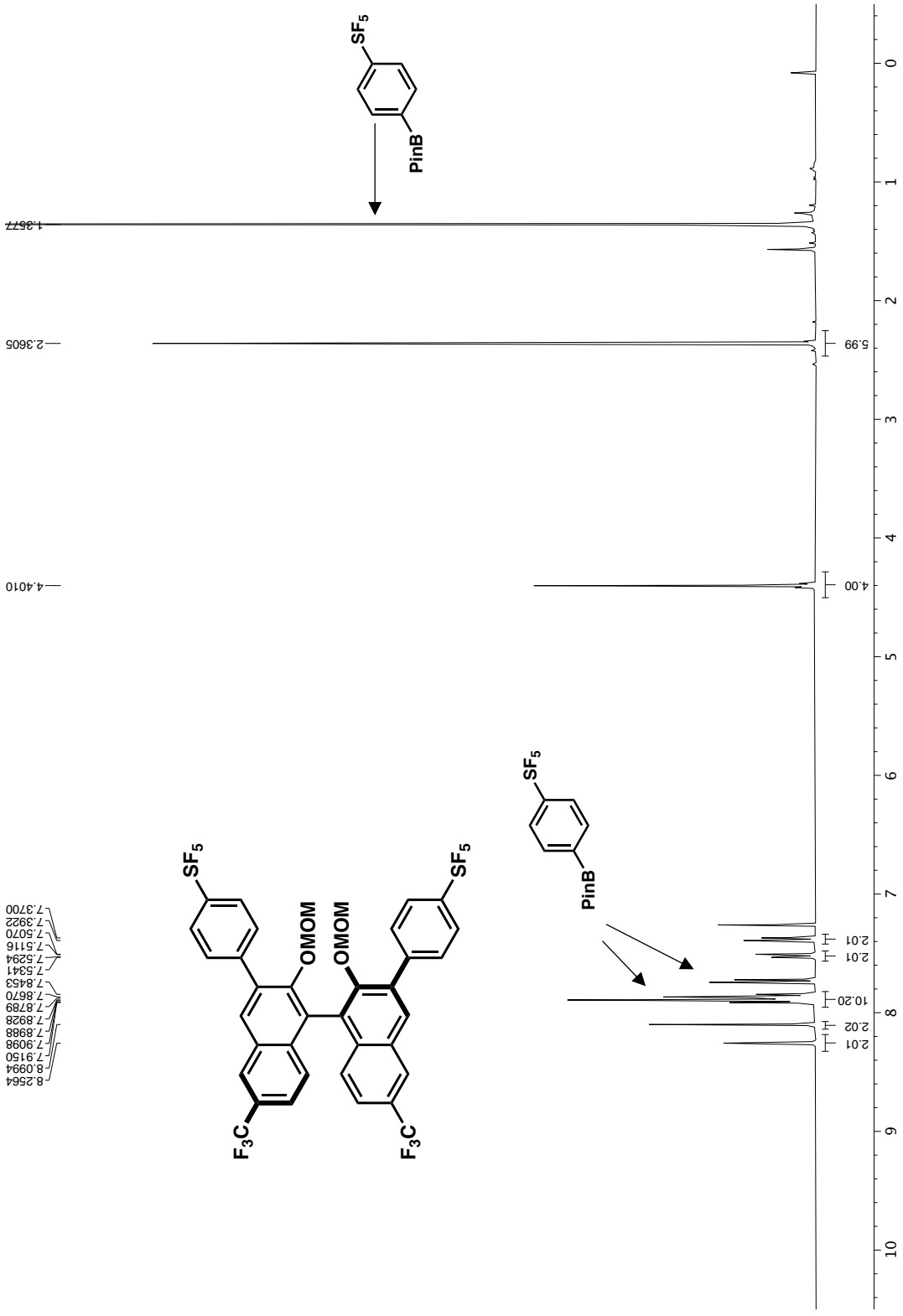
^{19}F NMR (376 MHz, $CDCl_3$) of **212h**.



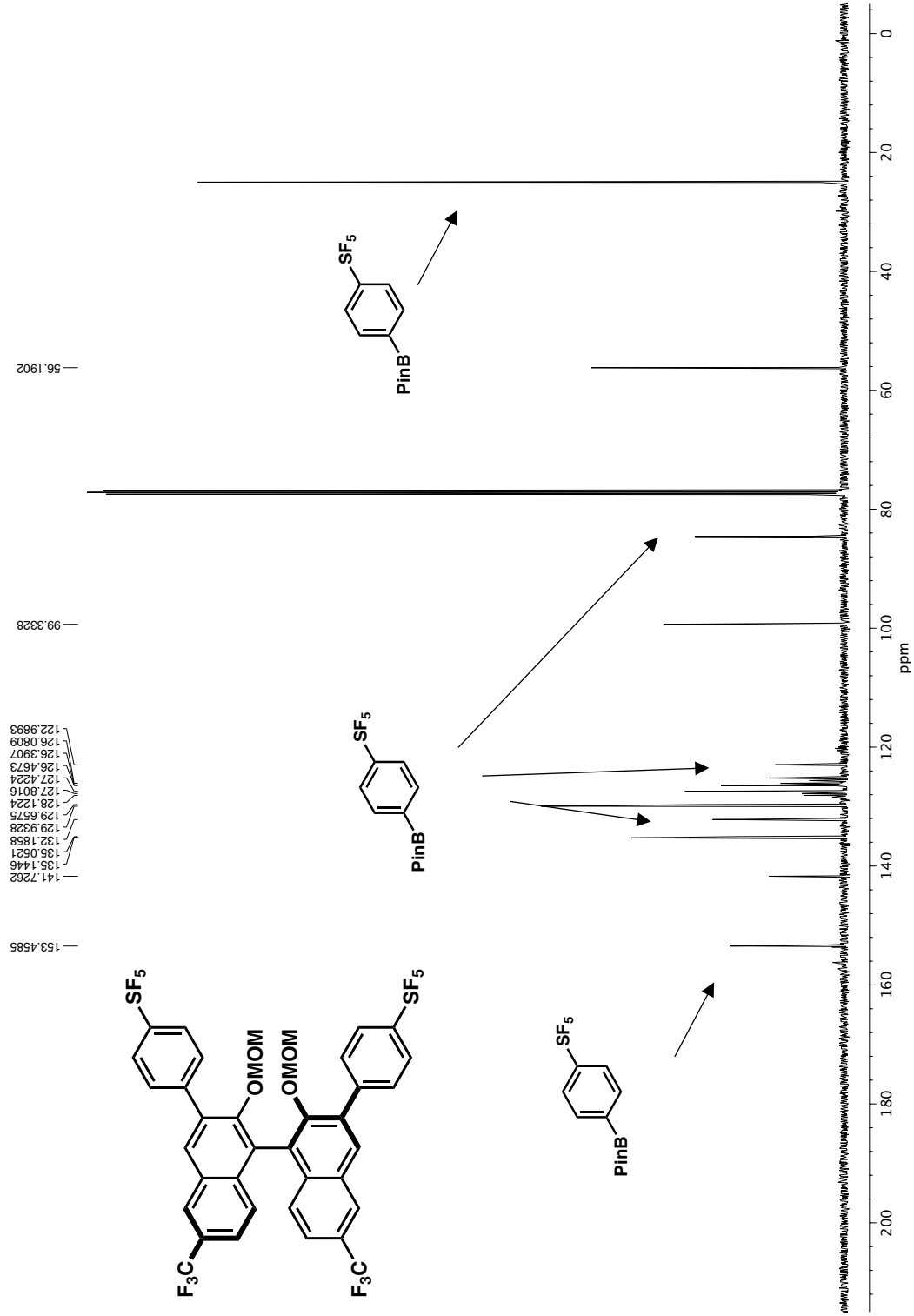
COSY NMR (400 MHz, $CDCl_3$) of **212h**.



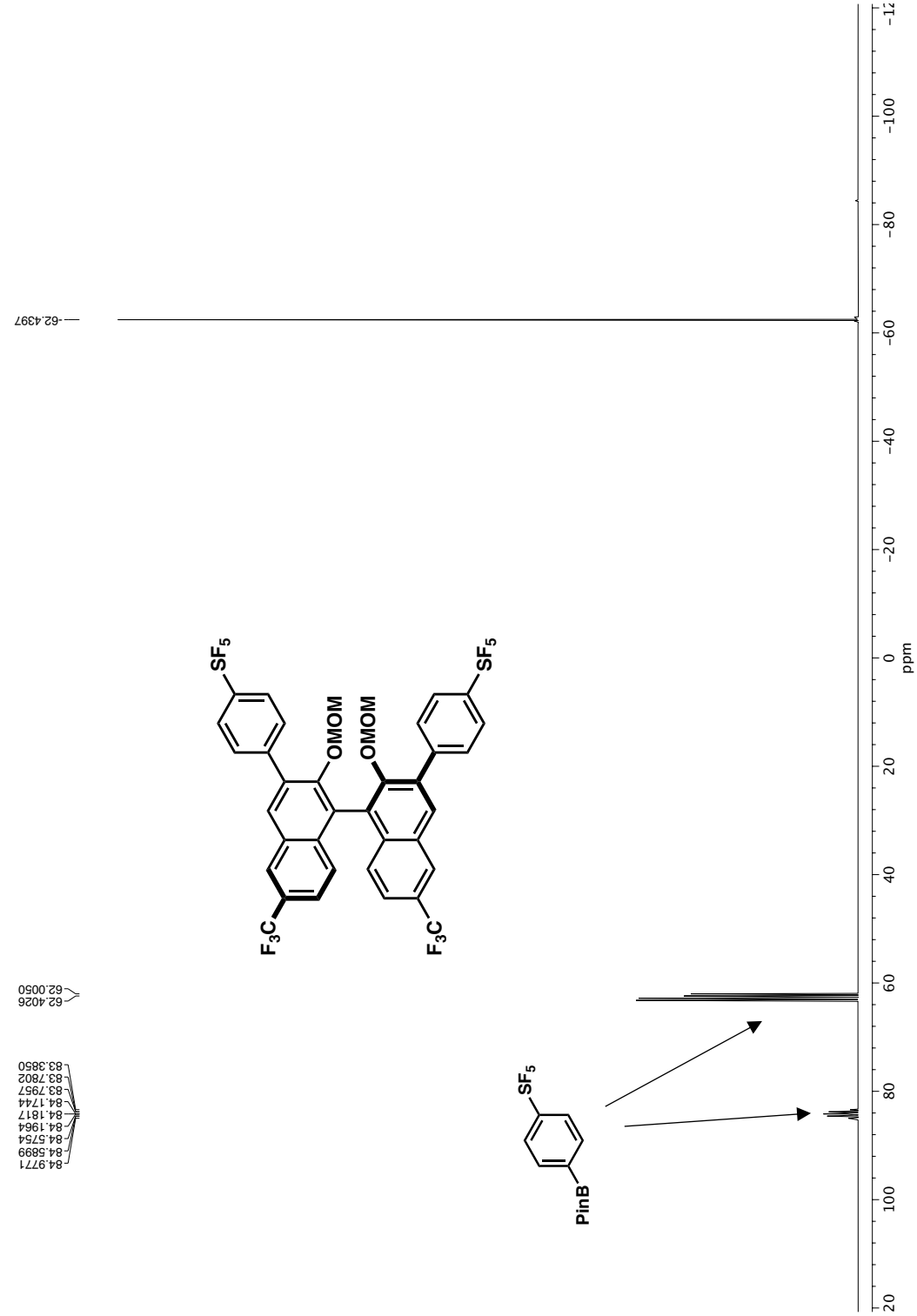
NOESY NMR (400 MHz, $CDCl_3$) of **212h**.



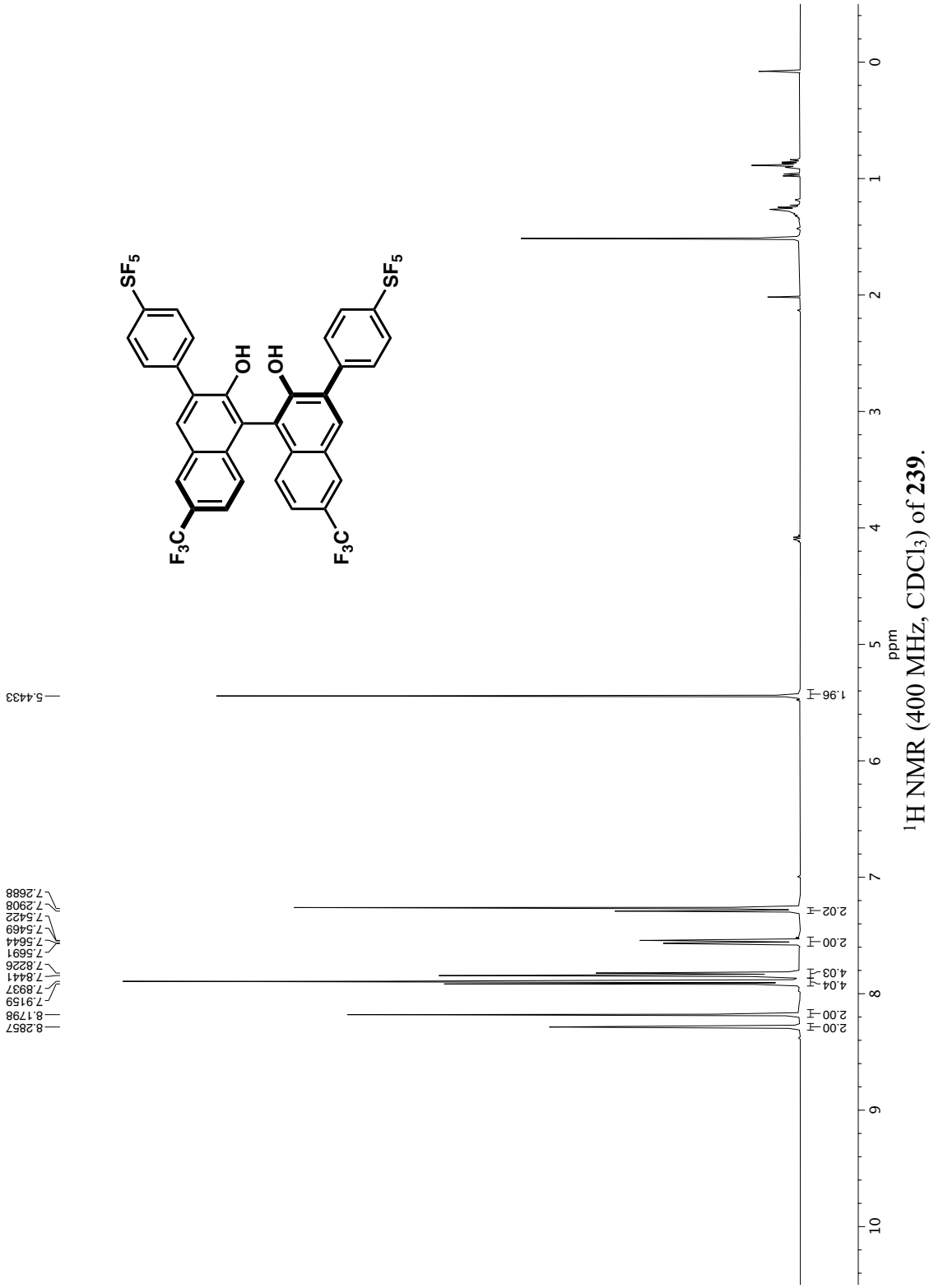
^{1}H NMR (400 MHz, $CDCl_3$) of **238**.



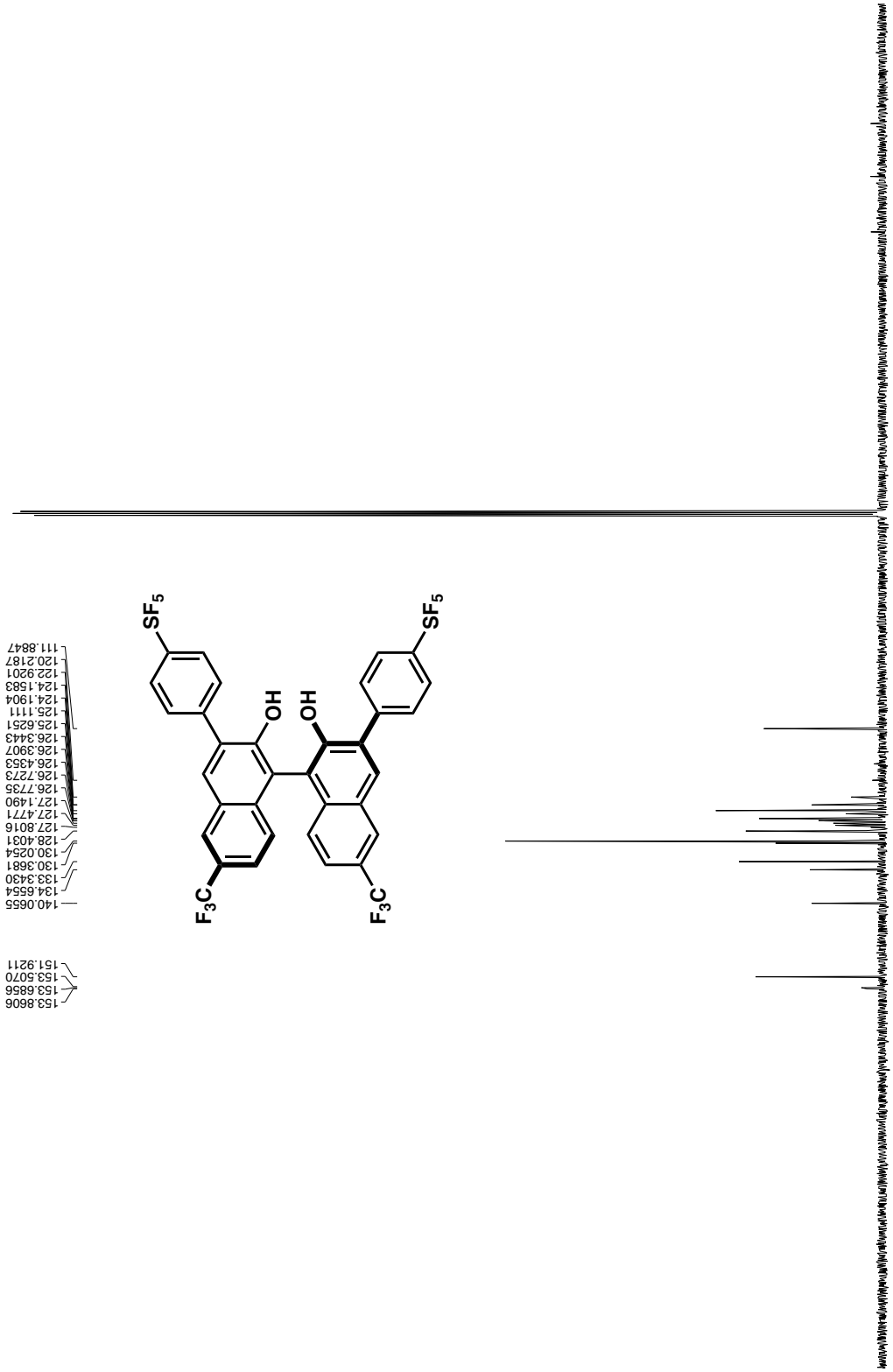
^{13}C NMR (101 MHz, $CDCl_3$) of **238**



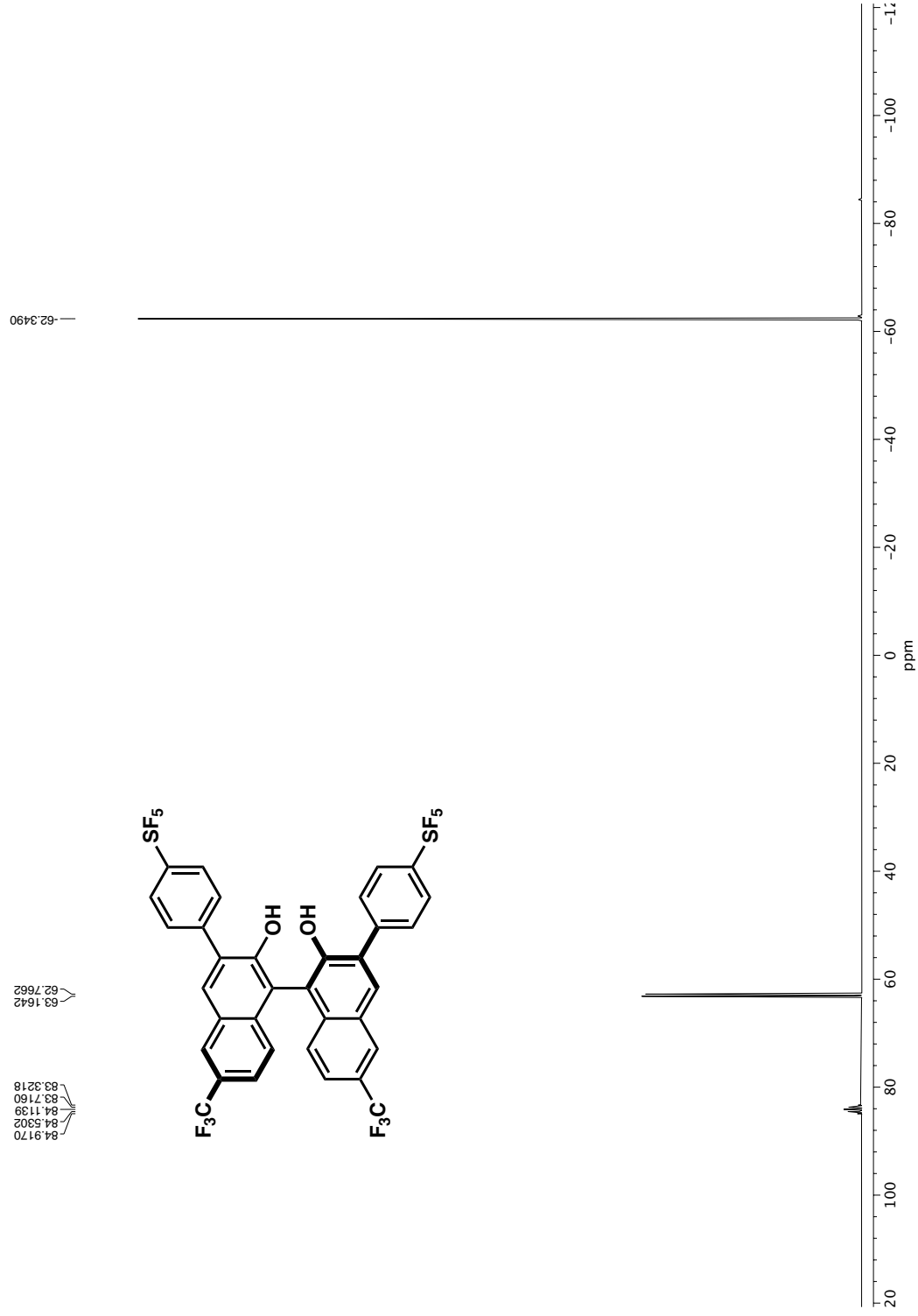
^{19}F NMR (376 MHz, $CDCl_3$) of **238**.



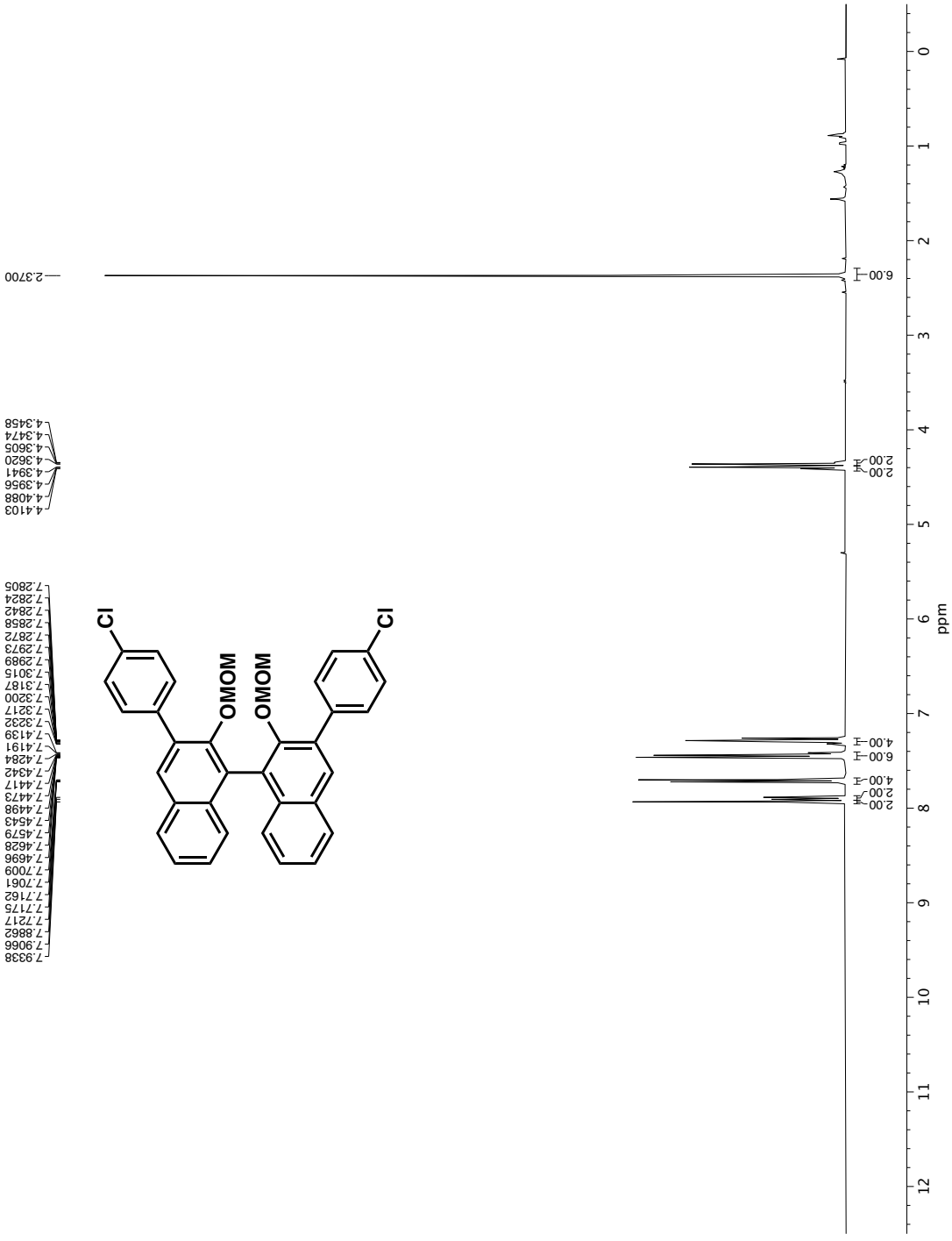
^{1}H NMR (400 MHz, $CDCl_3$) of **239**.



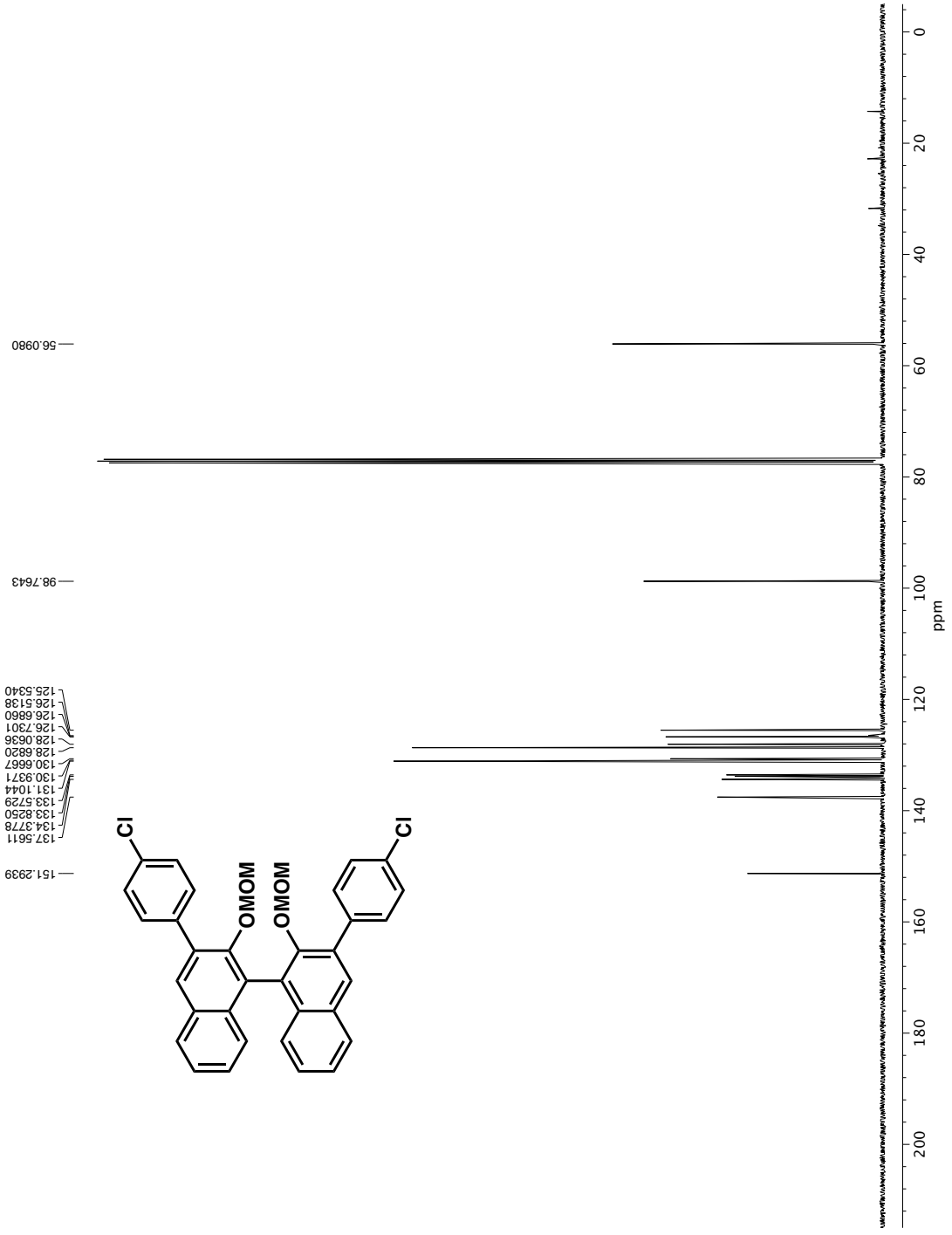
^{13}C NMR (101 MHz, $CDCl_3$) of **239**.



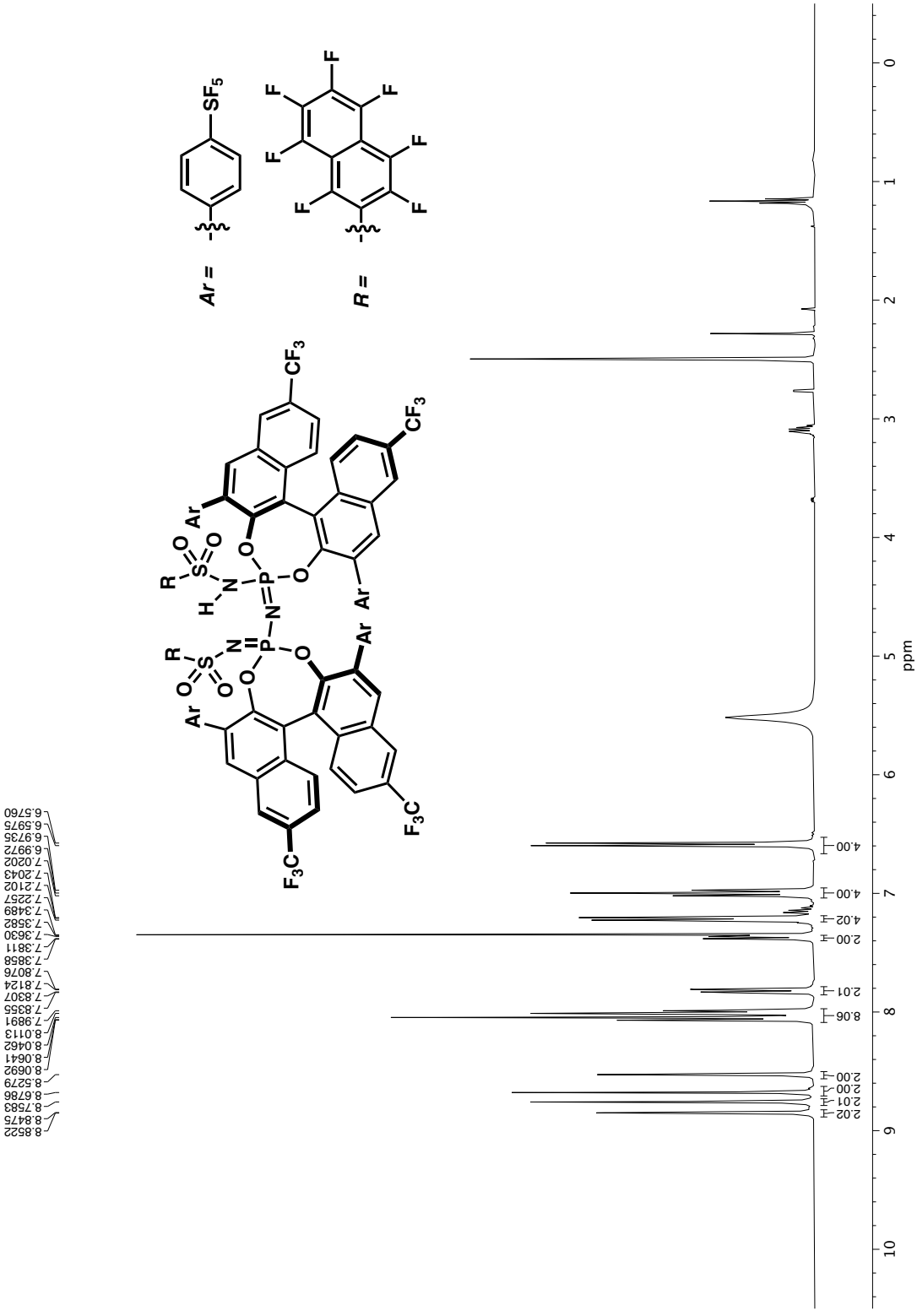
^{19}F NMR (376 MHz, $CDCl_3$) of **239**.



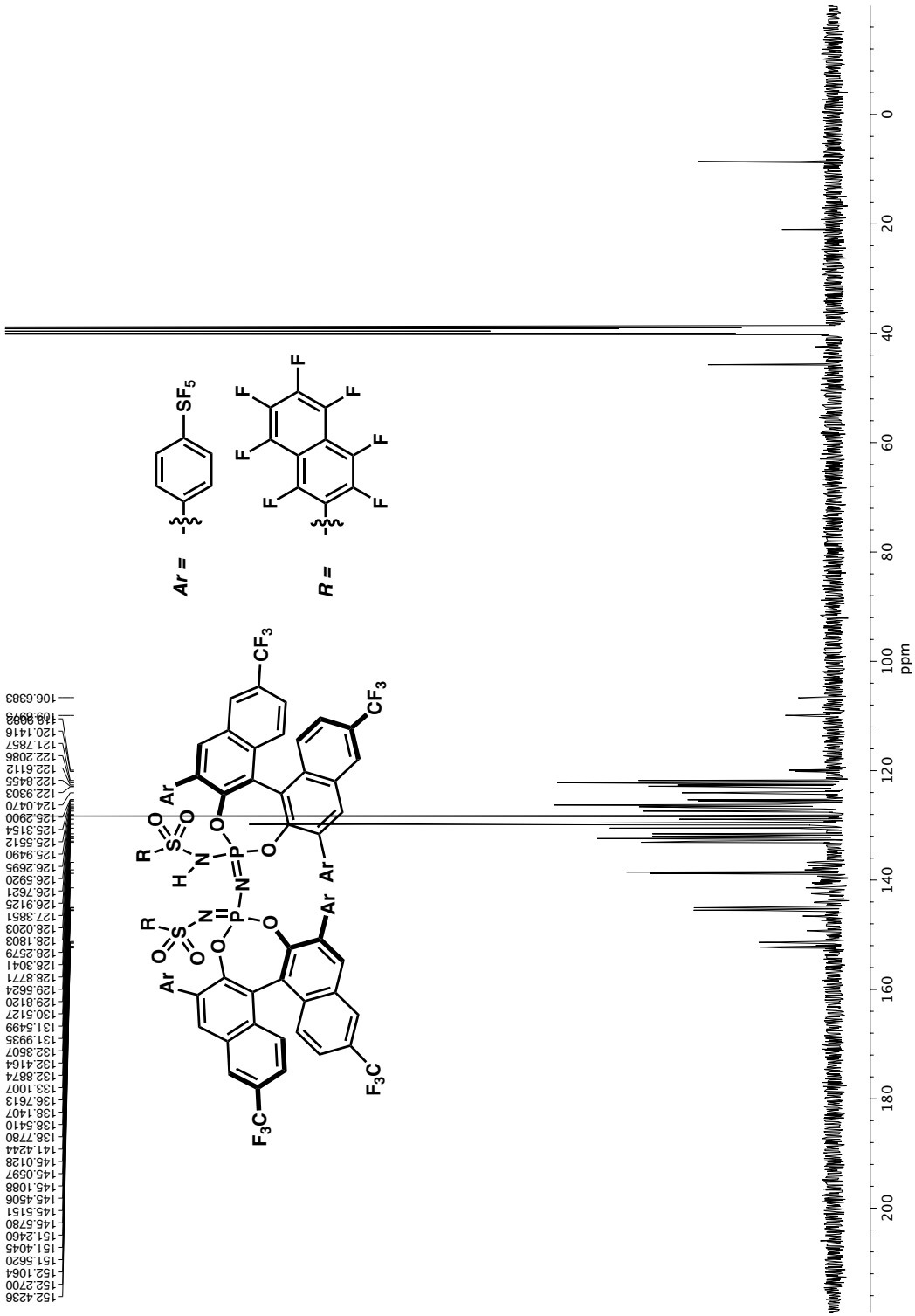
^{1}H NMR (400 MHz, $CDCl_3$) of **240**.



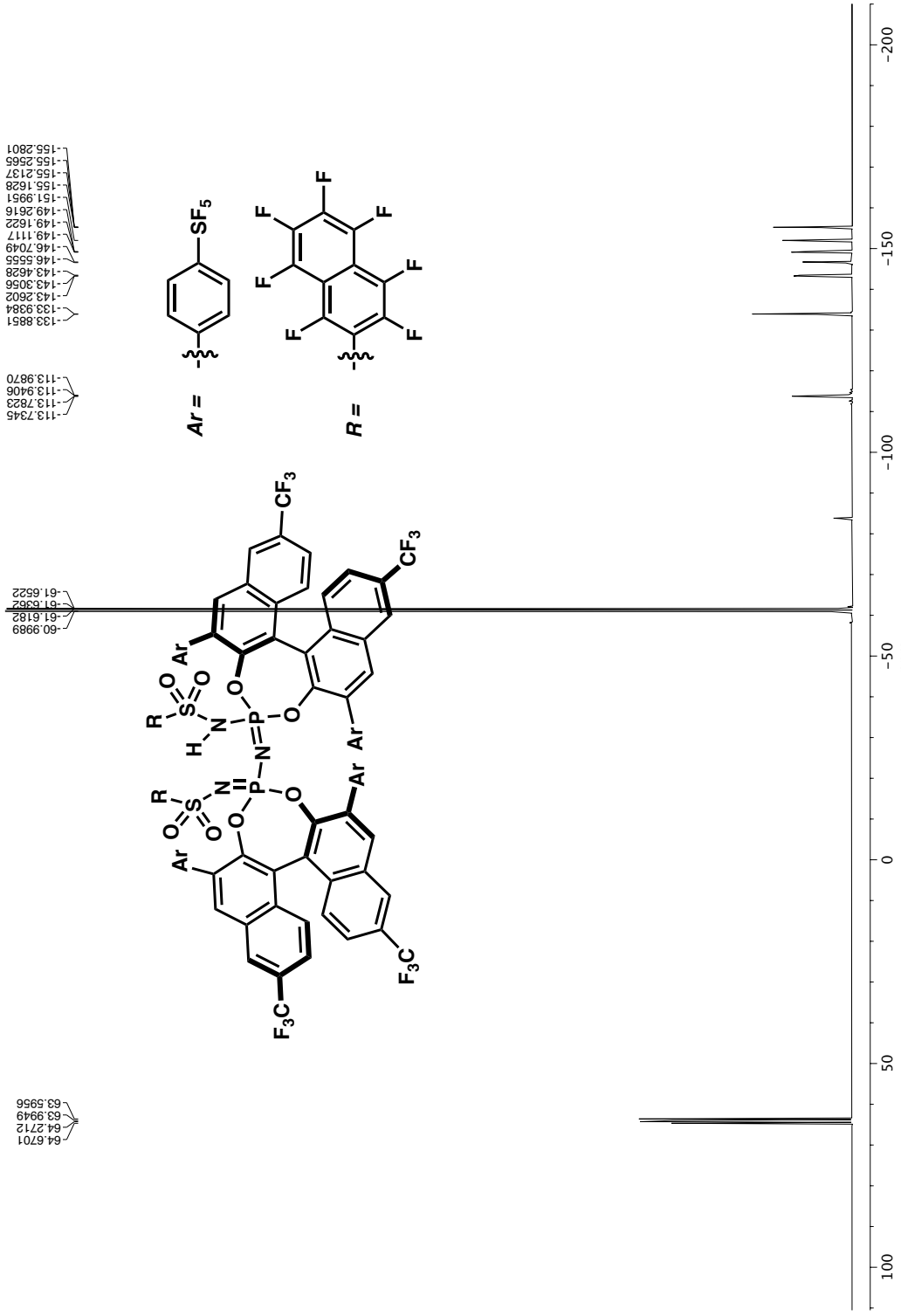
^{13}C NMR (101 MHz, $CDCl_3$) of **240**.



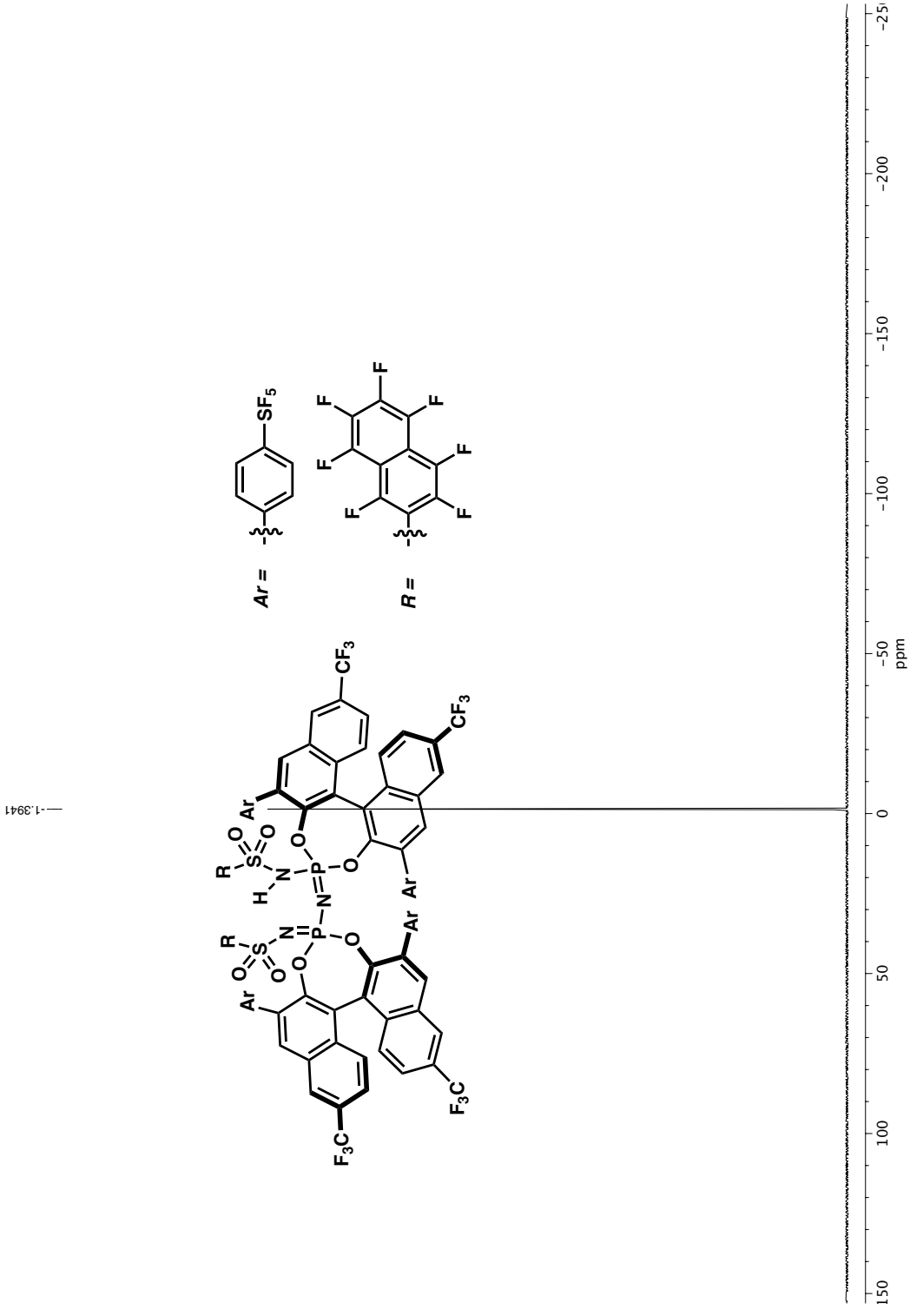
^{1}H NMR (400 MHz, d_6-DMSO) of **IDPI-211**.



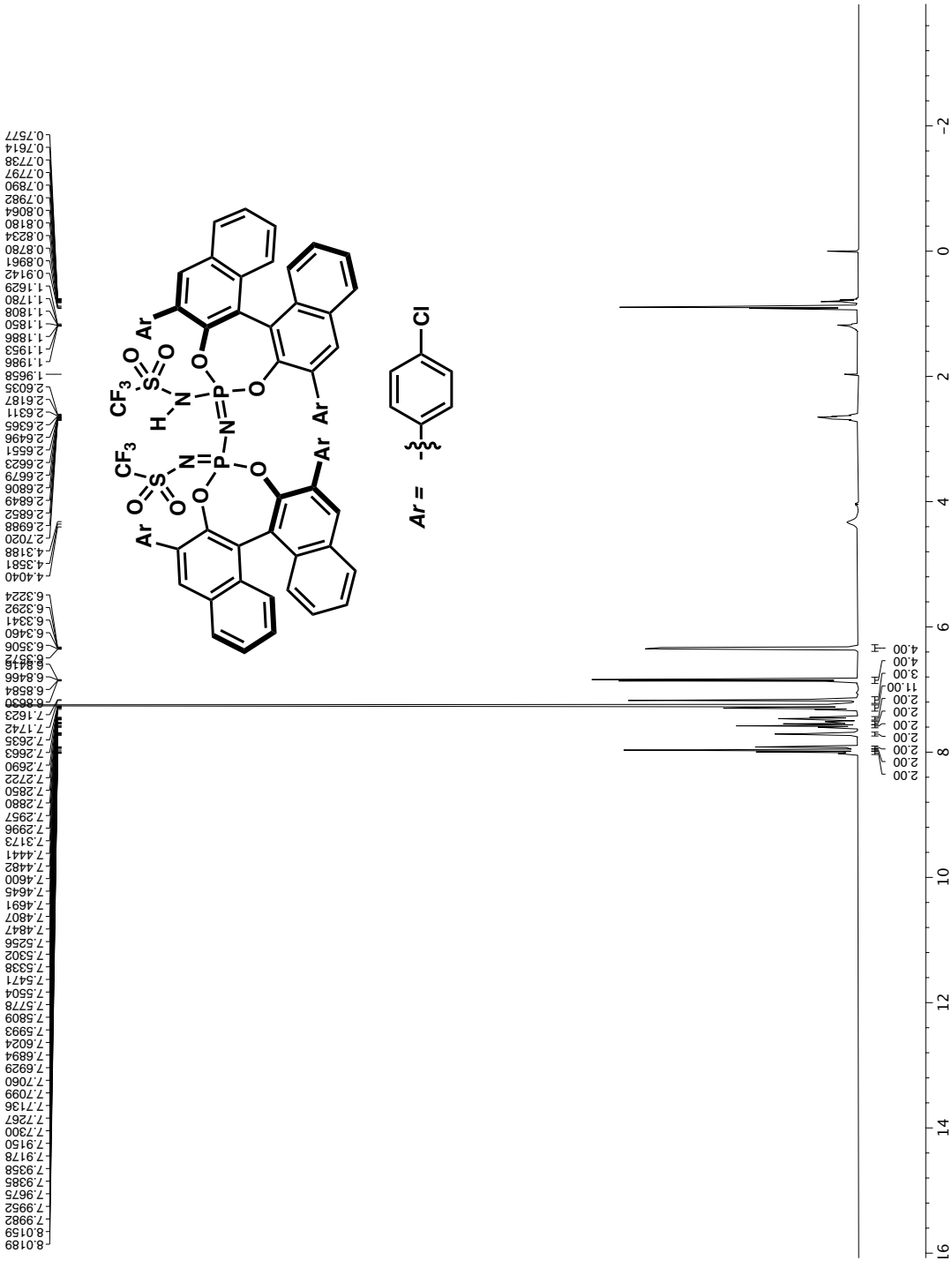
^{13}C NMR (101 MHz, d_6-DMSO) of **IDPI-211**.



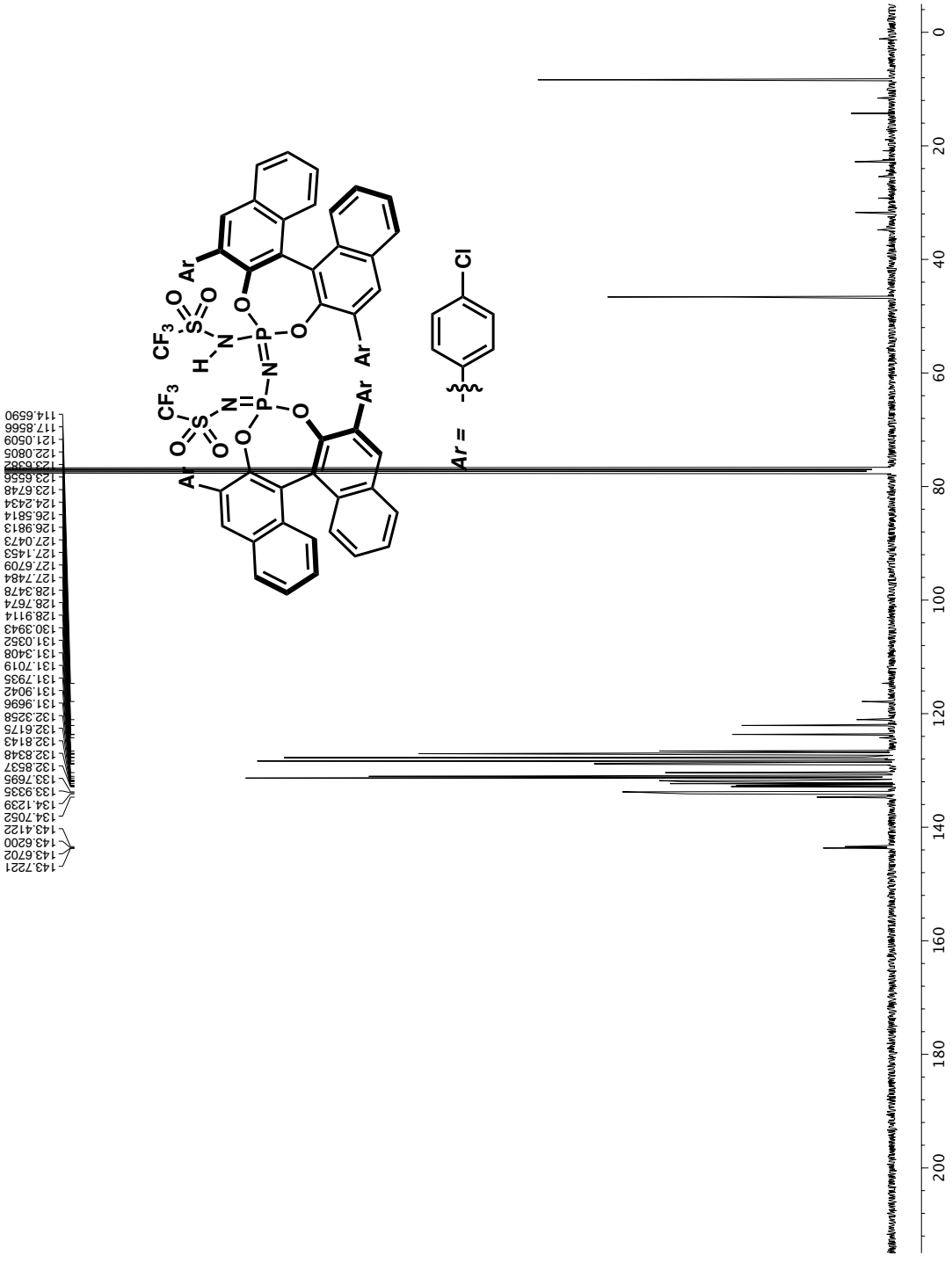
^{19}F NMR (376 MHz, d_6-DMSO) of **IDPI-211**.



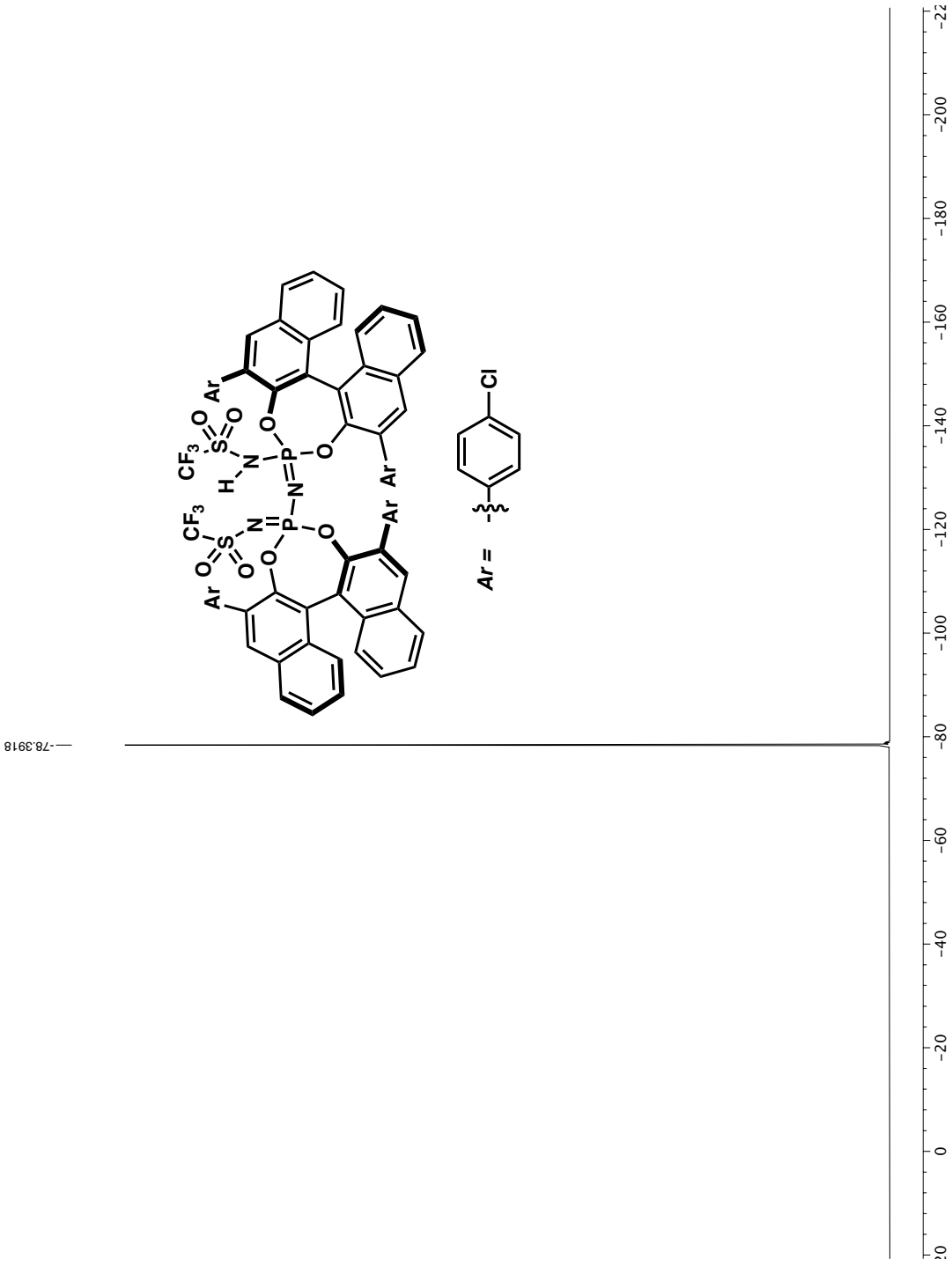
^{31}P NMR (161 MHz, d_6-DMSO) of **IDPI-211**.



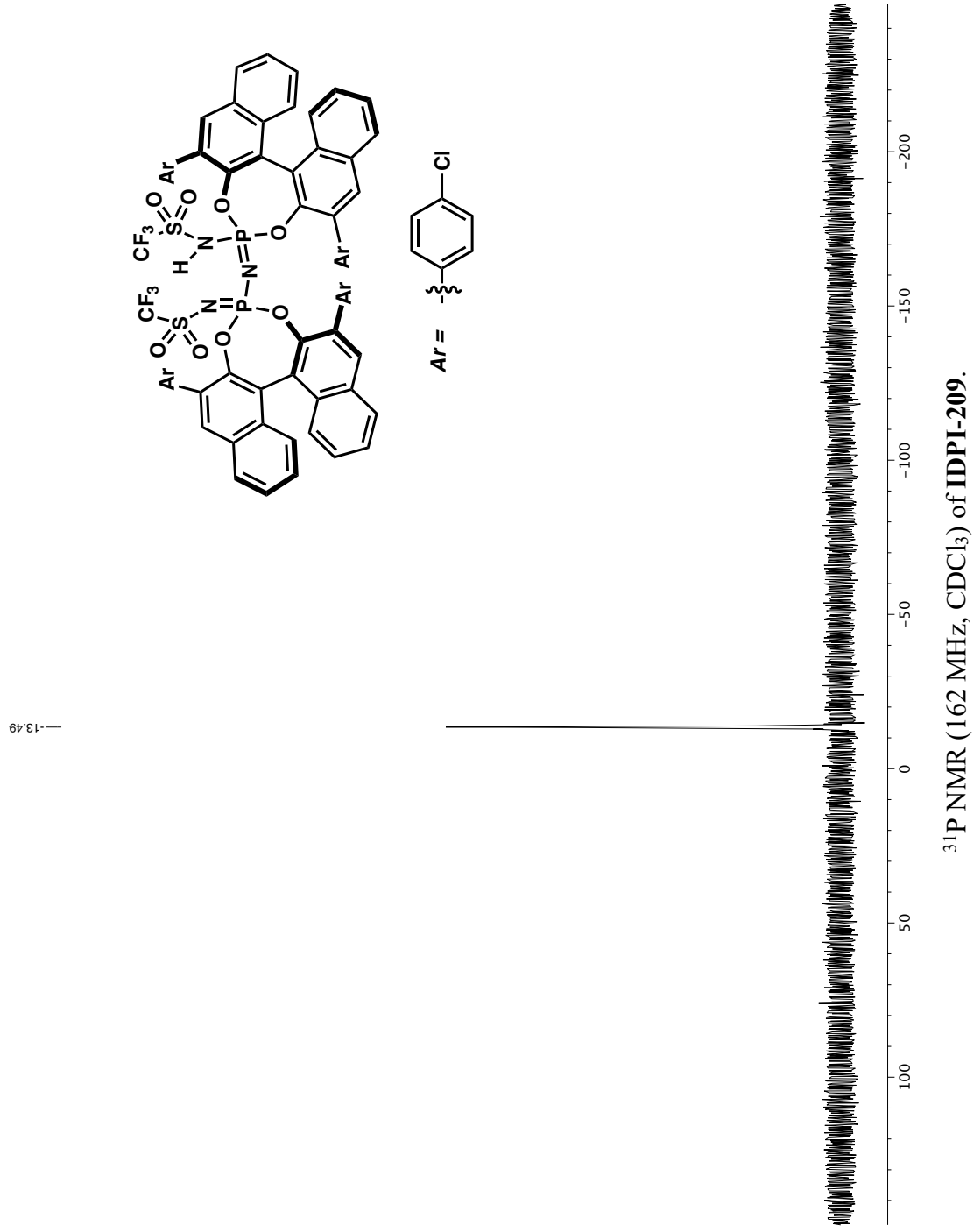
^{1}H NMR (400 MHz, $CDCl_3$) of **IDPI-209**.



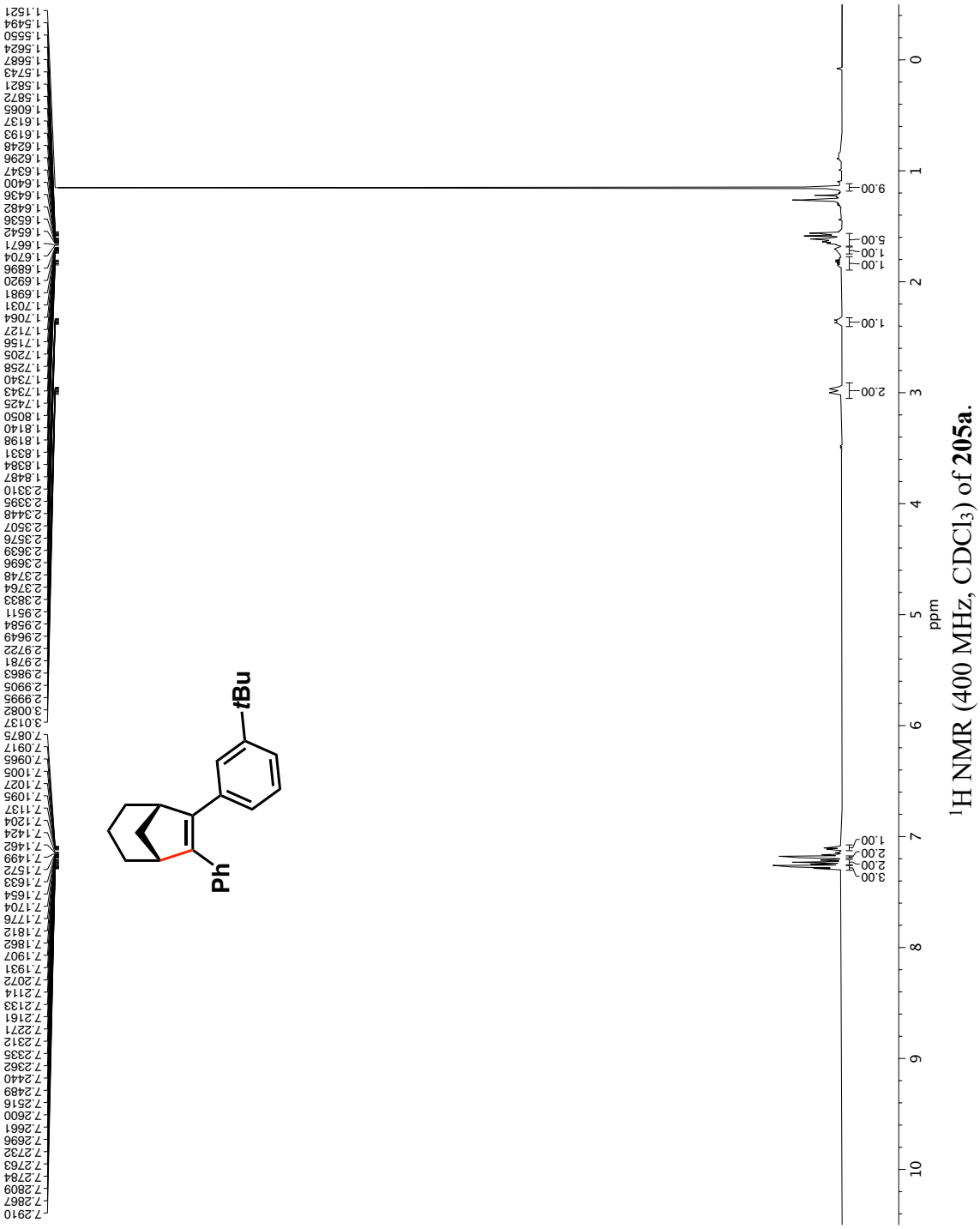
^{13}C NMR (101 MHz, $CDCl_3$) of **IDPI-209**.



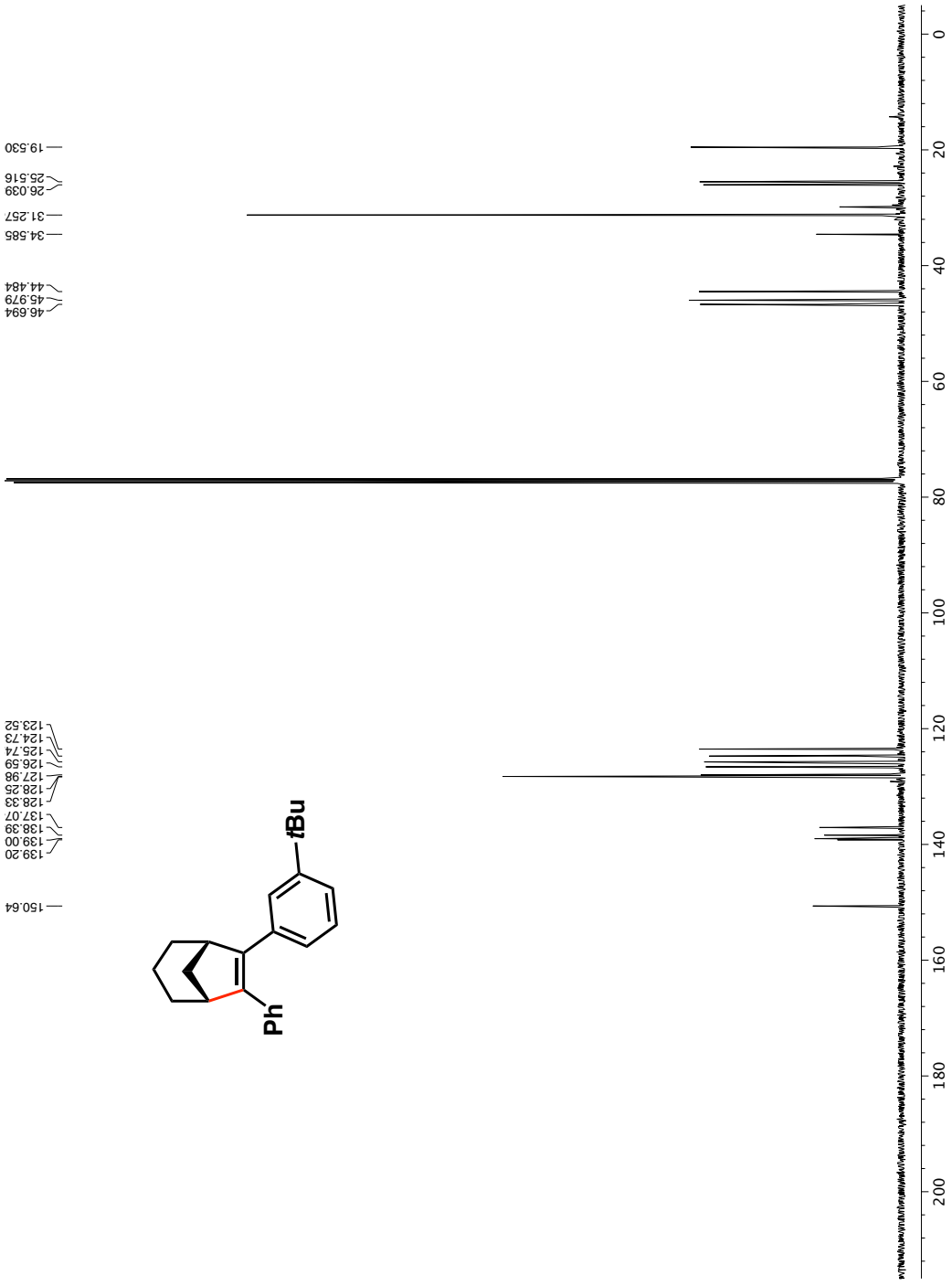
^{19}F NMR (376 MHz, $CDCl_3$) of **IDPI-209**.



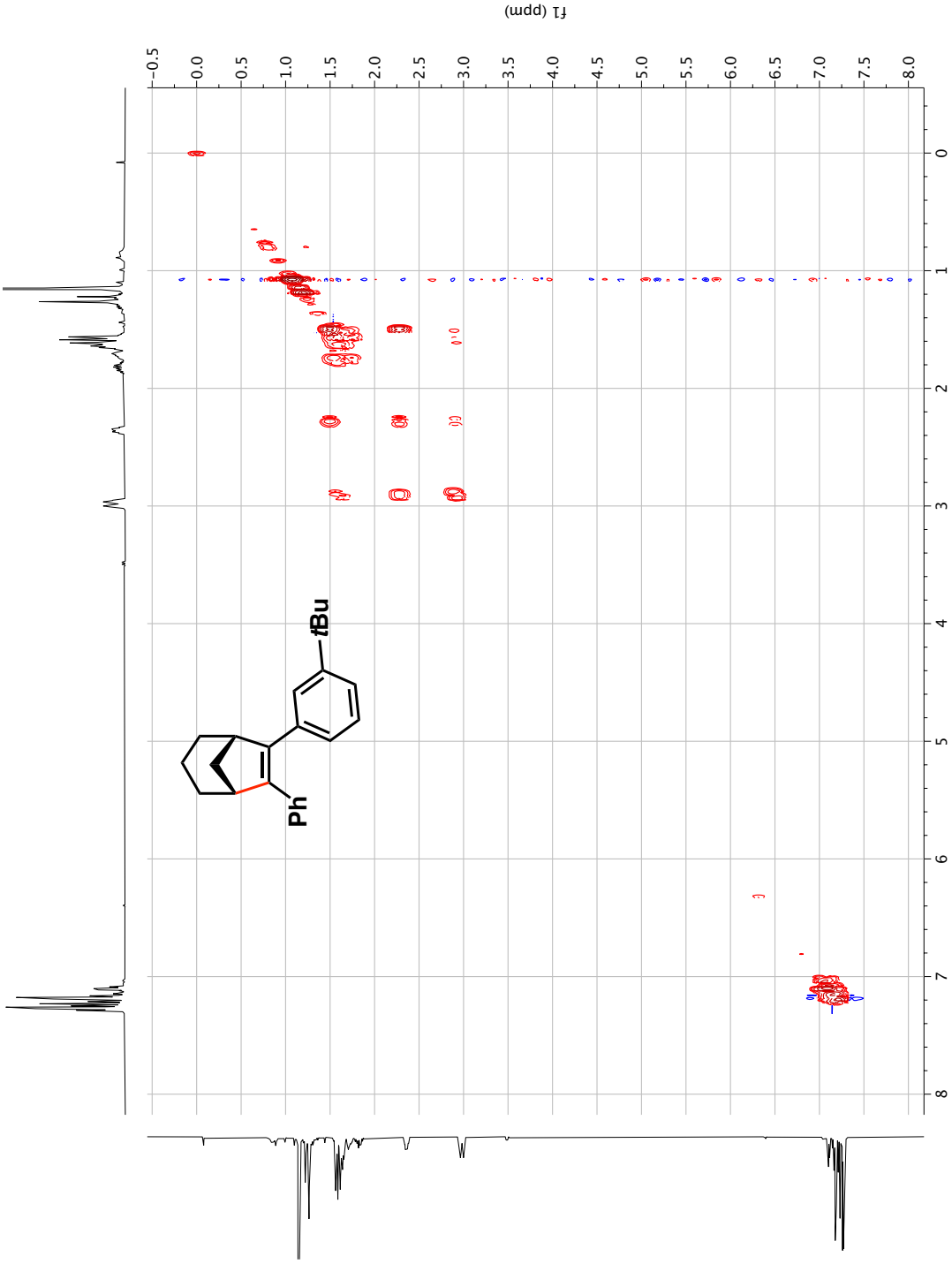
^{31}P NMR (162 MHz, $CDCl_3$) of **IDPI-209**.



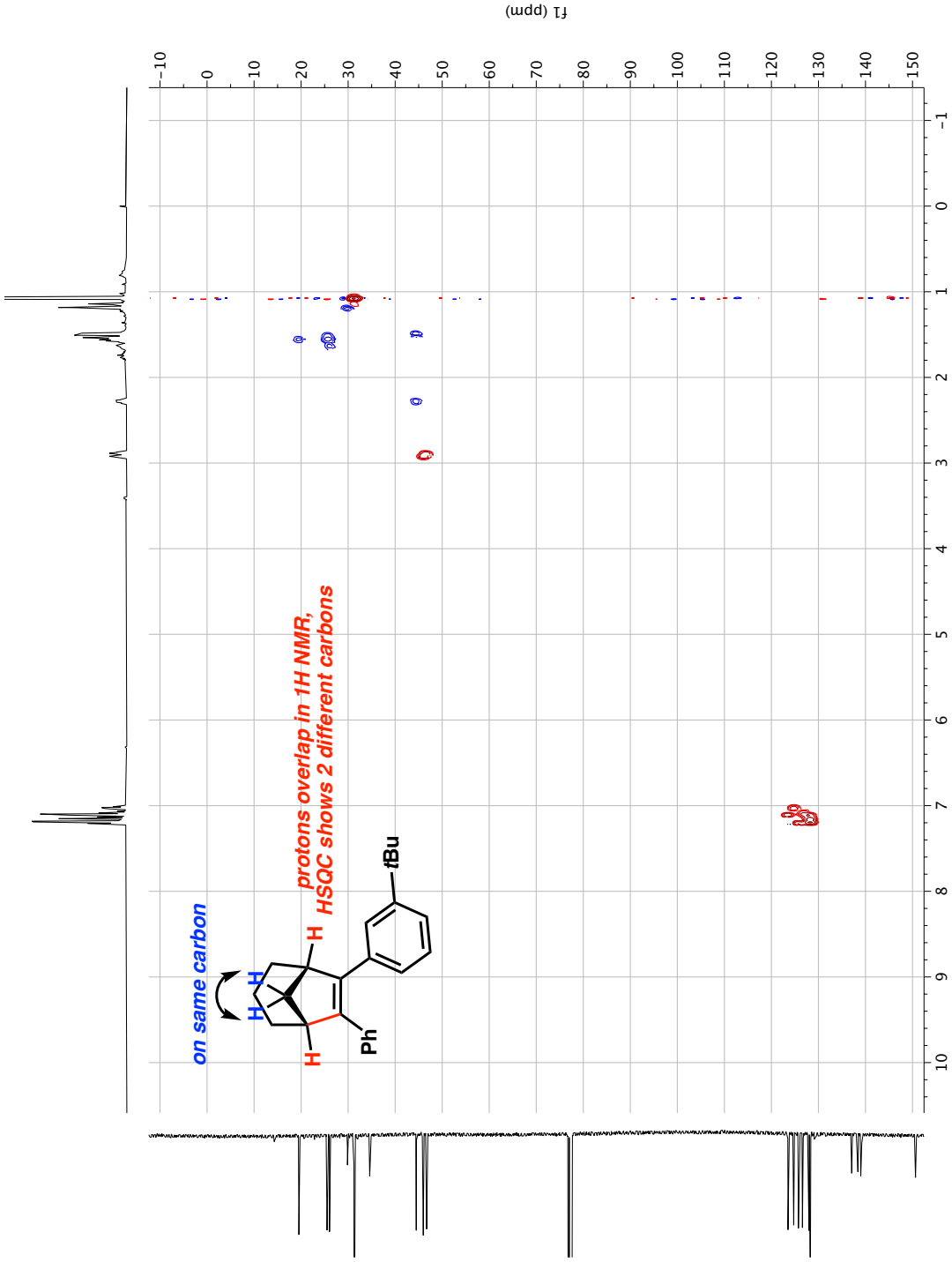
^{1}H NMR (400 MHz, $CDCl_3$) of **205a**.



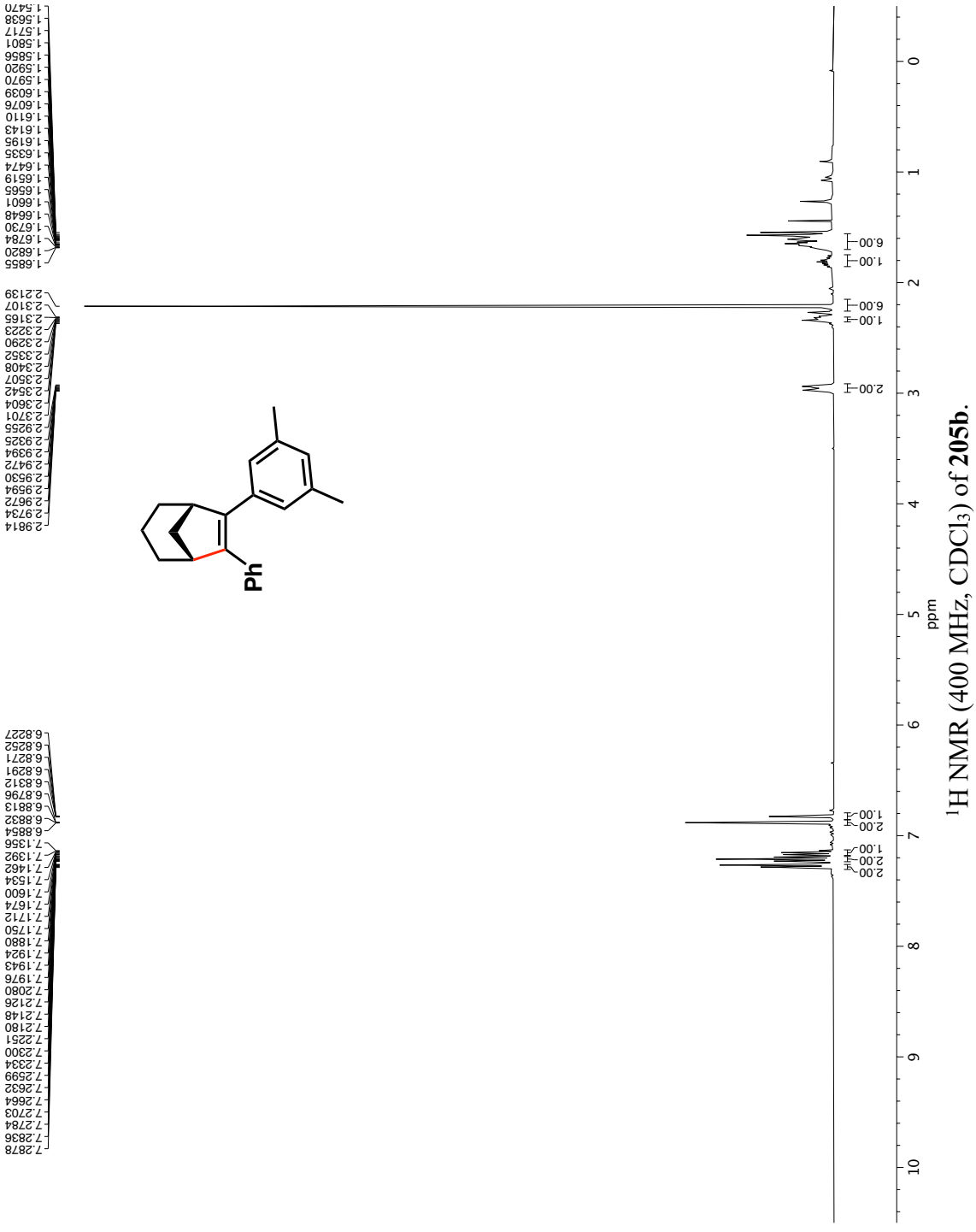
^{13}C NMR (101 MHz, $CDCl_3$) of **205a**.



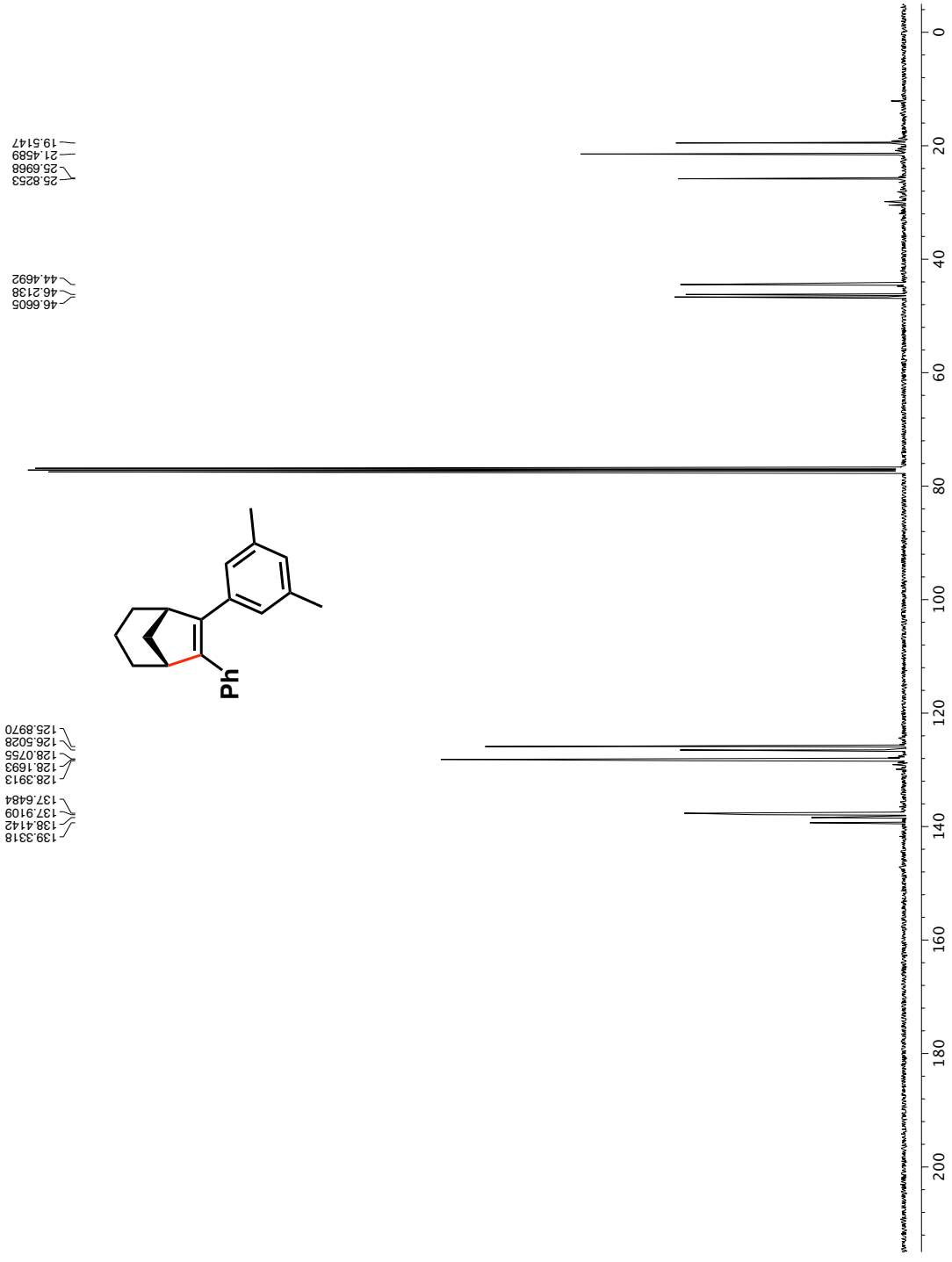
COSY NMR (400 MHz, $CDCl_3$) of **205a**.



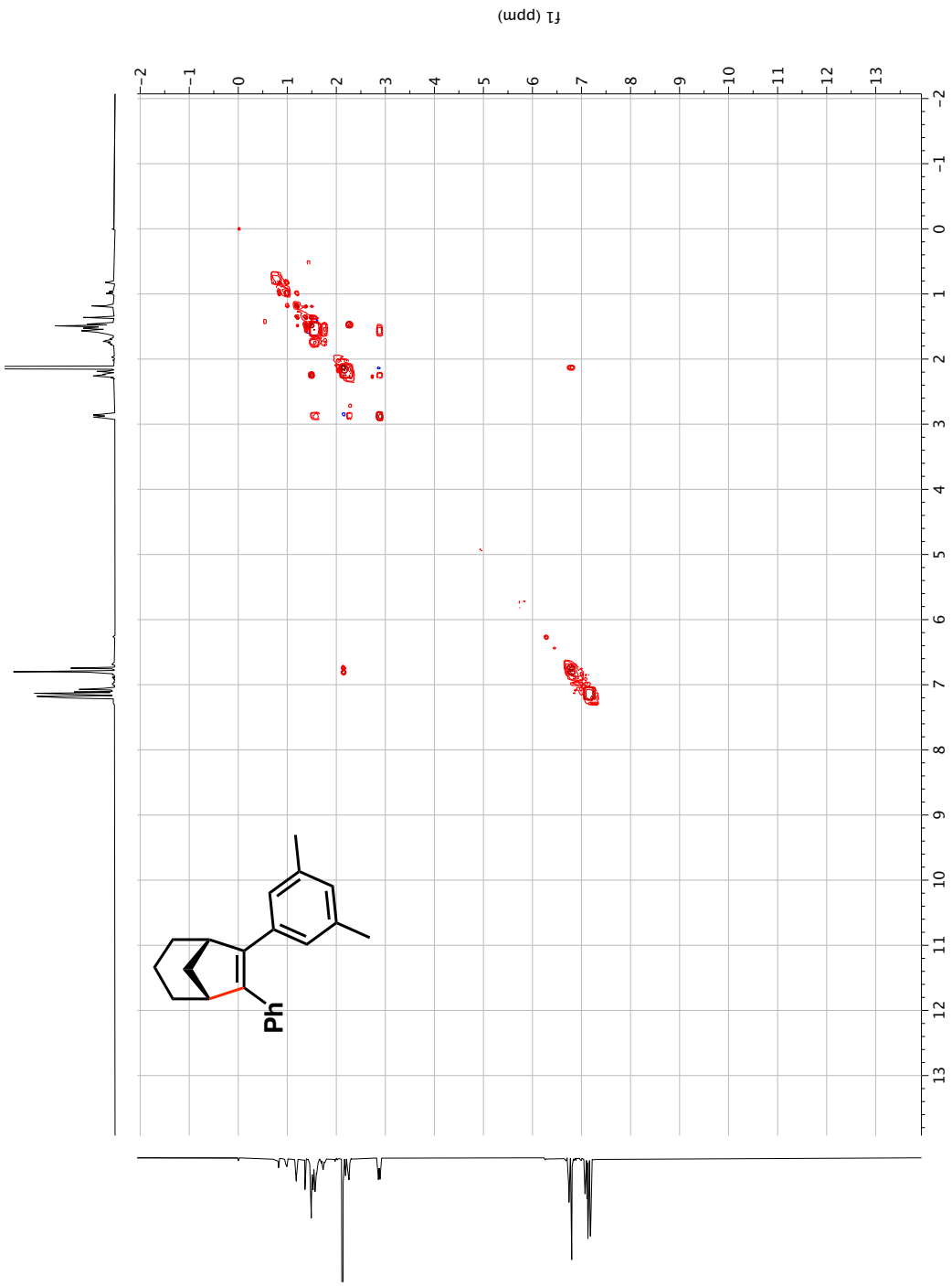
HSQC NMR (400 MHz, $CDCl_3$) of **205a**.



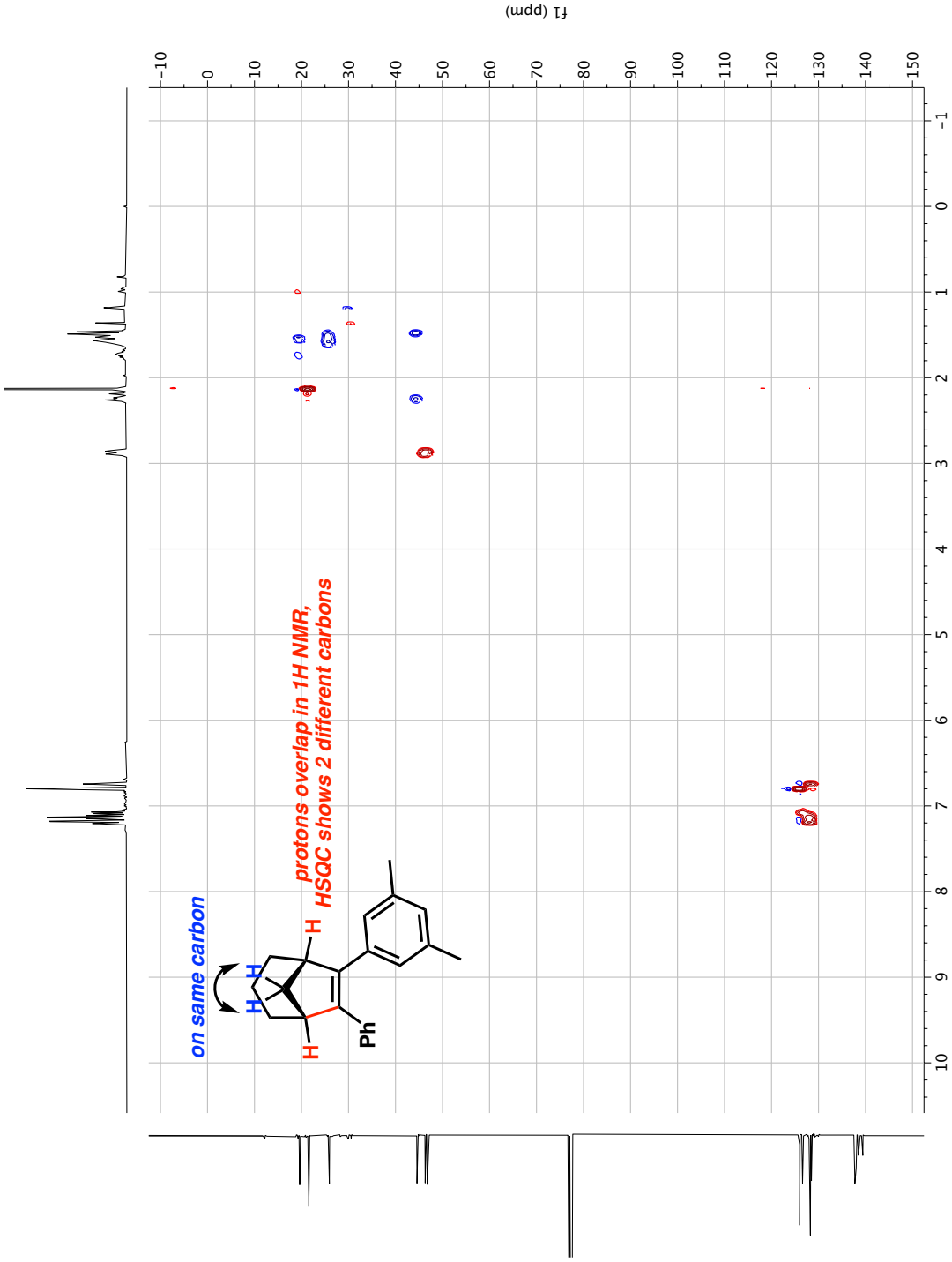
^{1}H NMR (400 MHz, $CDCl_3$) of **205b**.



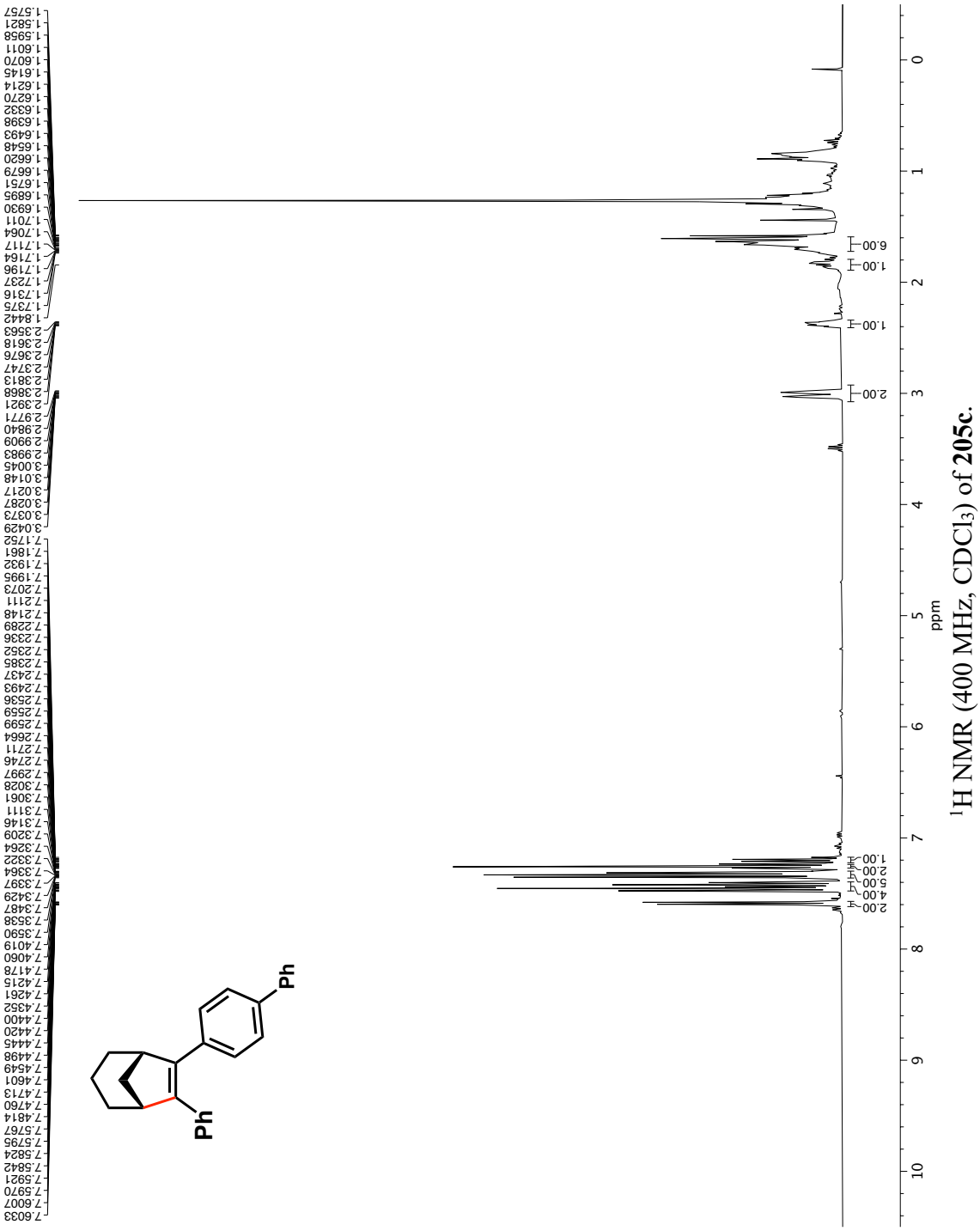
^{13}C NMR (101 MHz, $CDCl_3$) of **205b**.



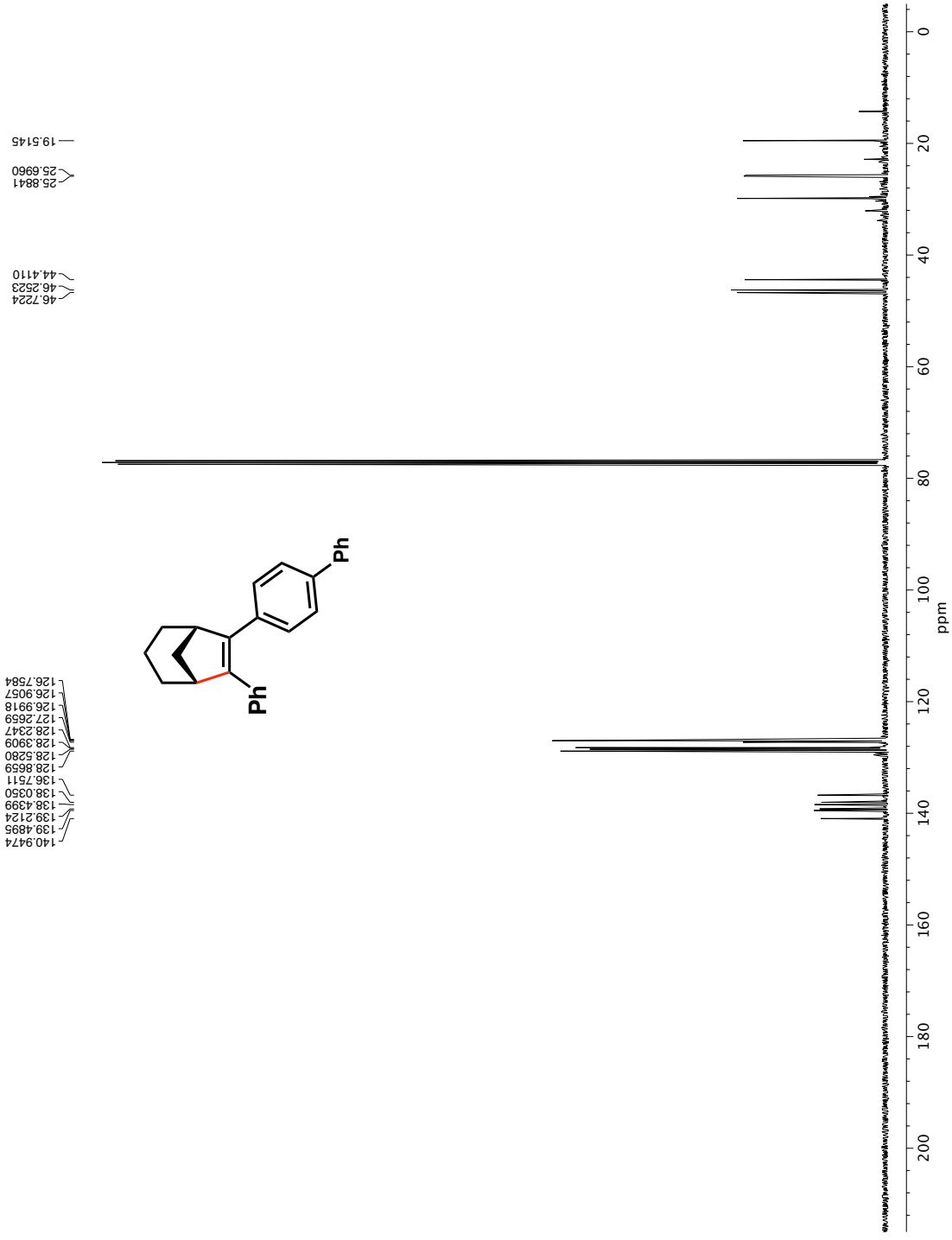
COSY NMR (400 MHz, $CDCl_3$) of **205b**.



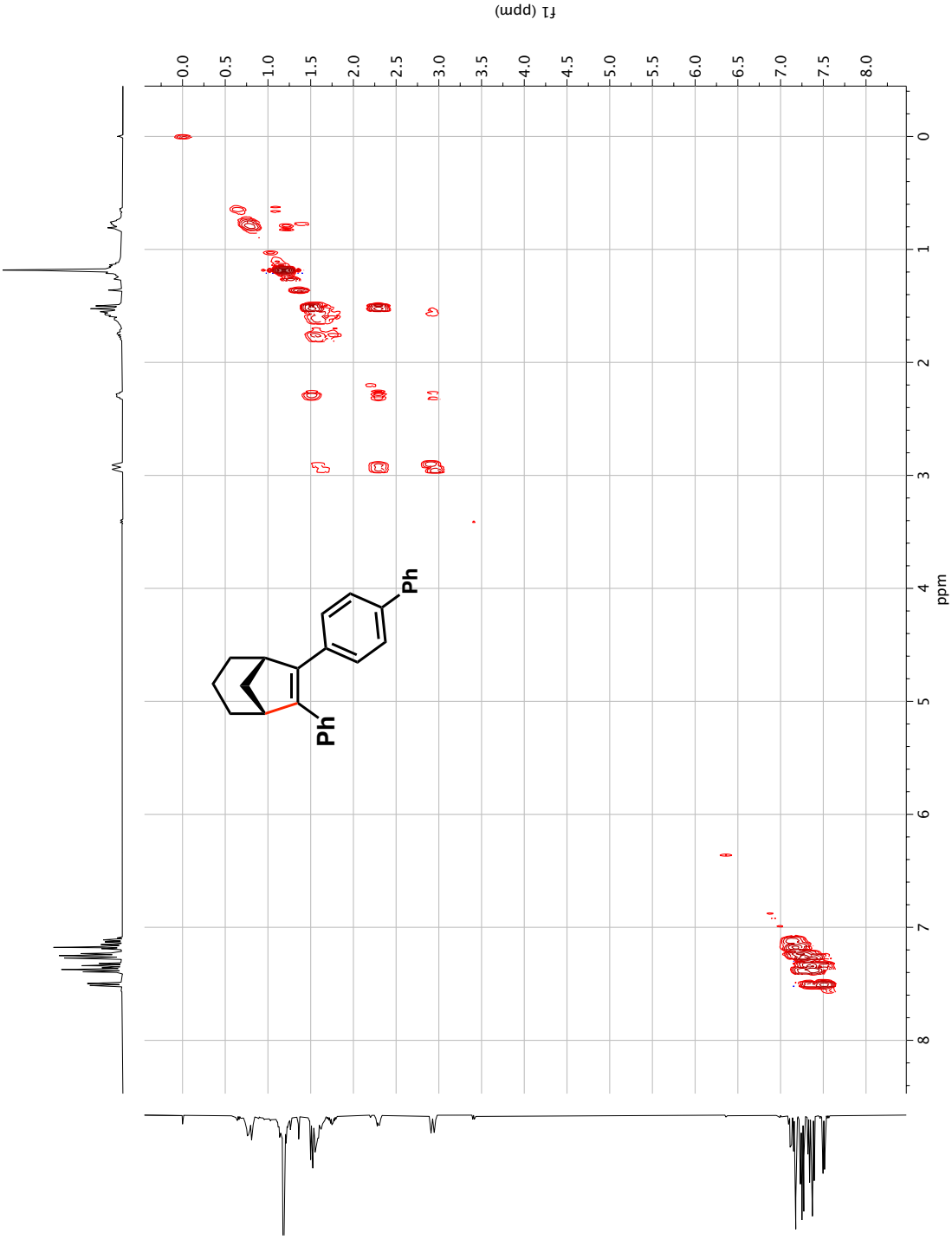
HSQC NMR (400 MHz, $CDCl_3$) of **205b**.



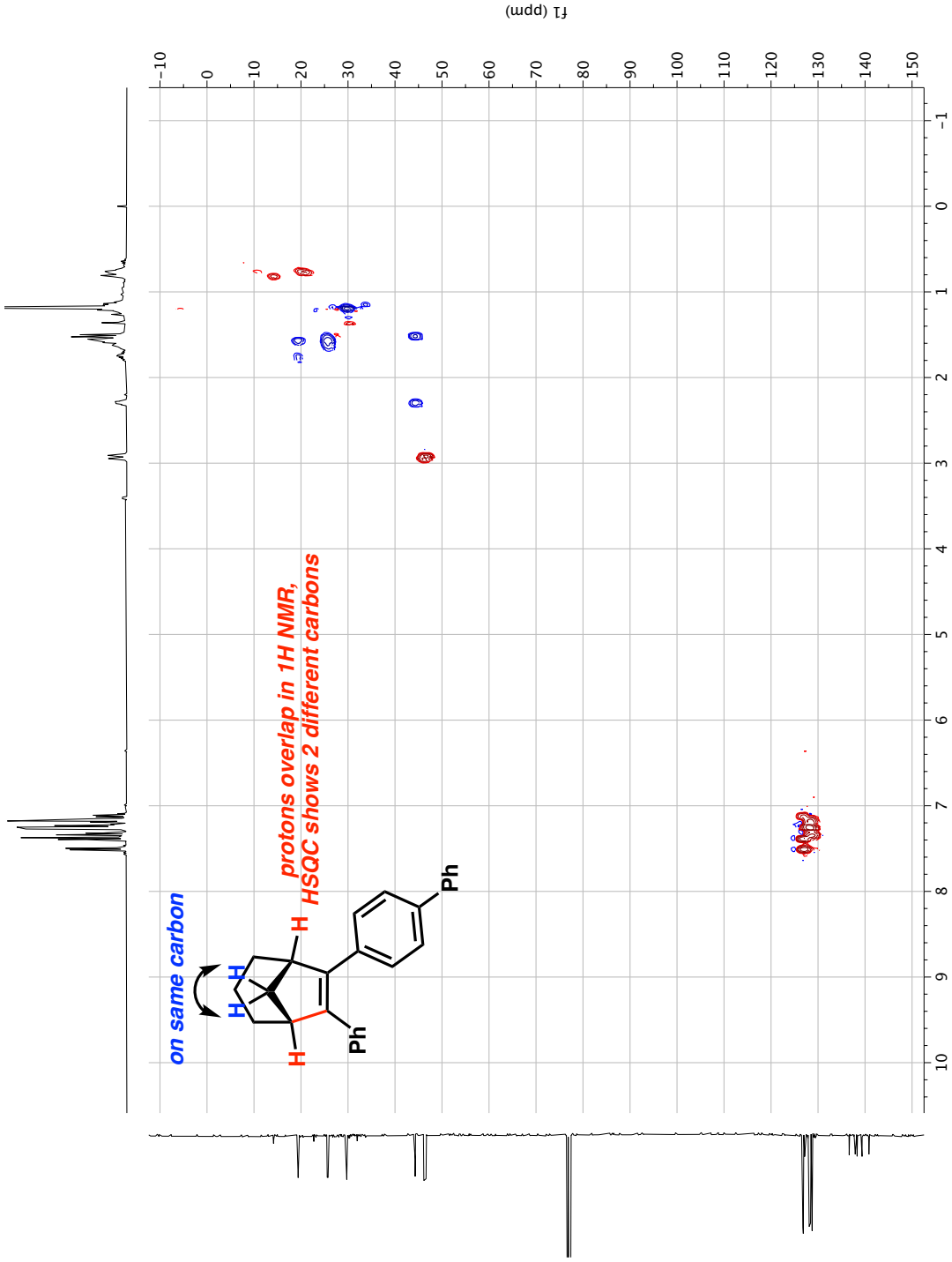
^{1}H NMR (400 MHz, $CDCl_3$) of **205c**.



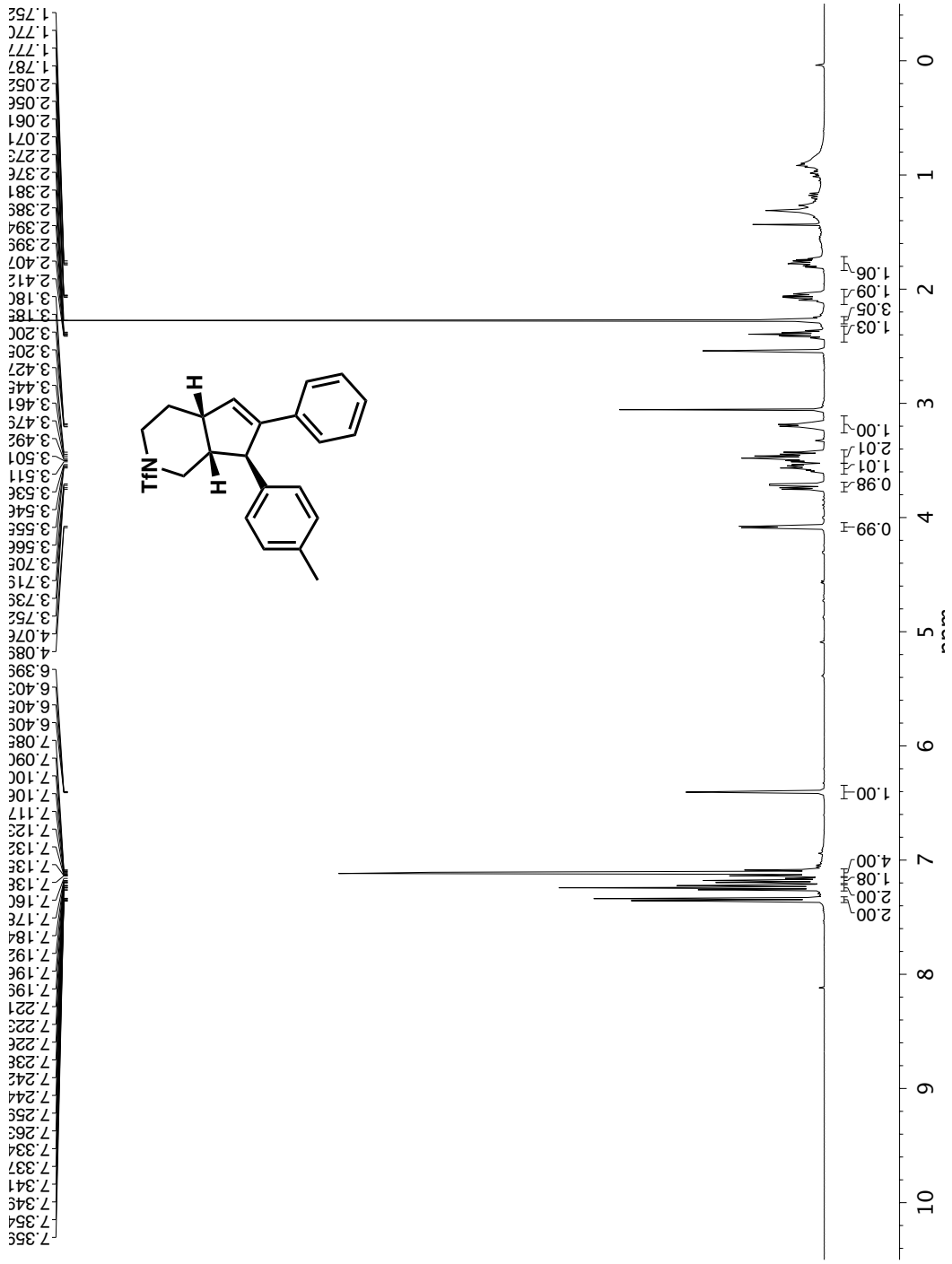
^{13}C NMR (101 MHz, $CDCl_3$) of **205c**.



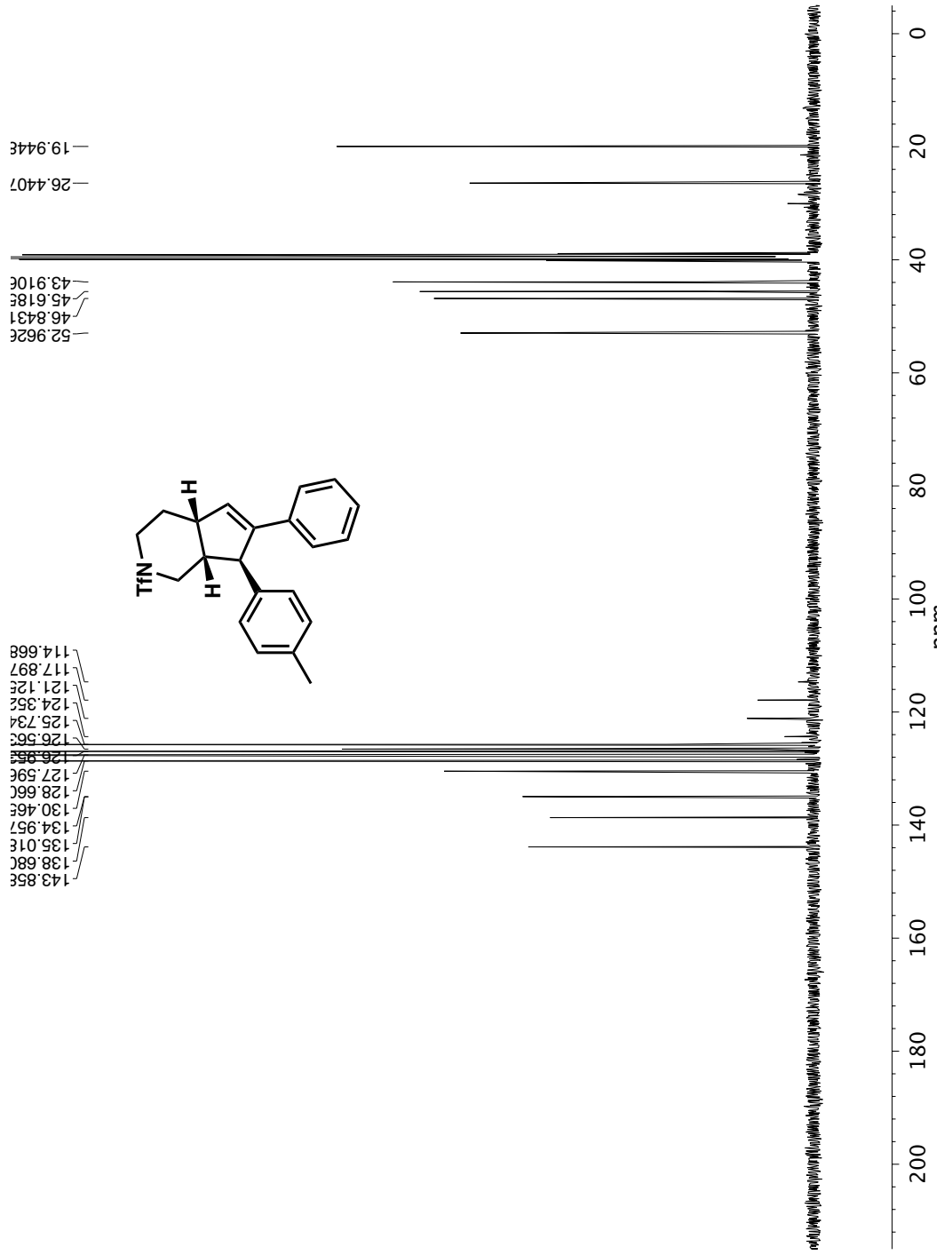
COSY NMR (400 MHz, $CDCl_3$) of **205c.**



HSQC NMR (400 MHz, $CDCl_3$) of **205c**.

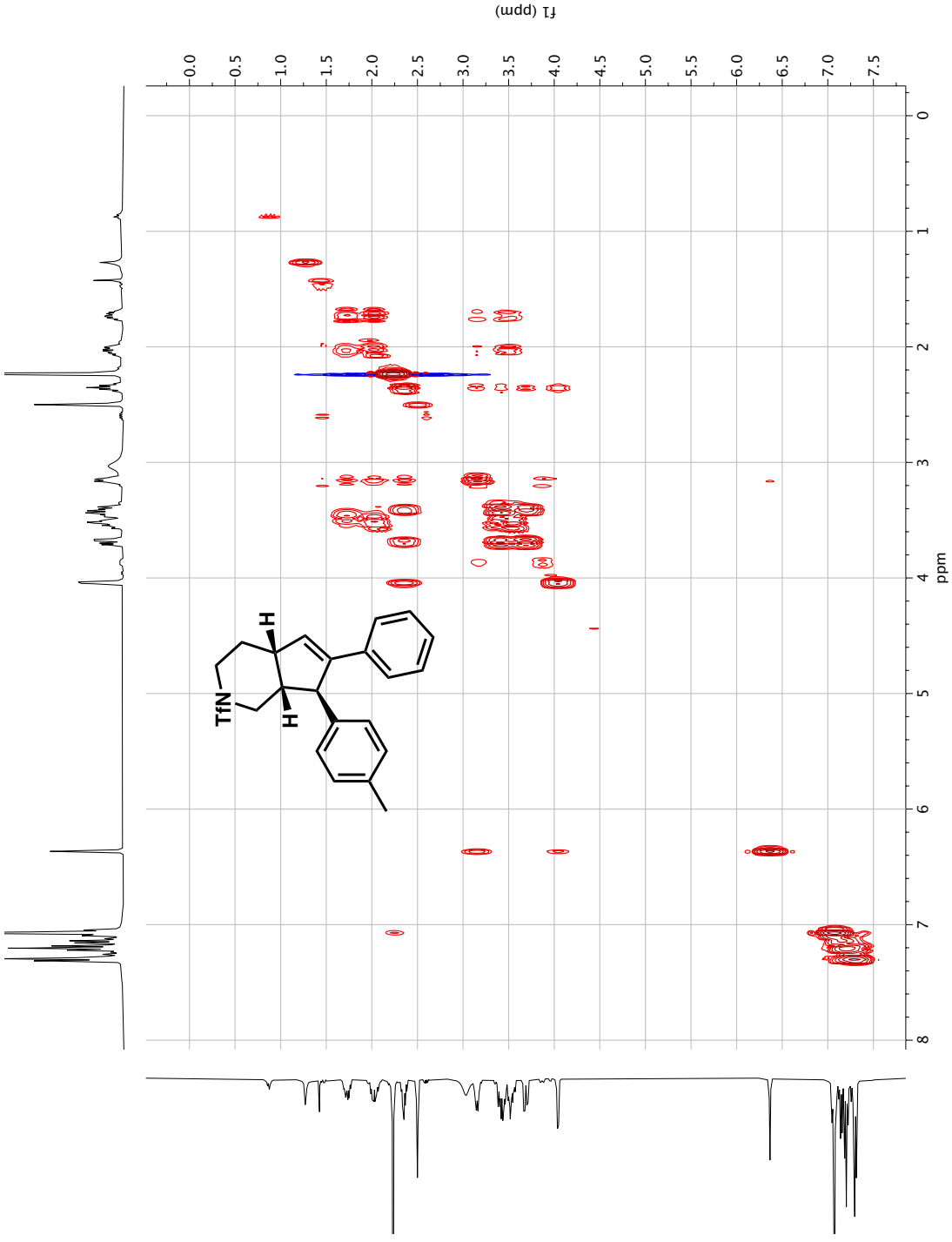


^{1}H NMR (400 MHz, d_6-DMSO, 90 °C) of **213a**.

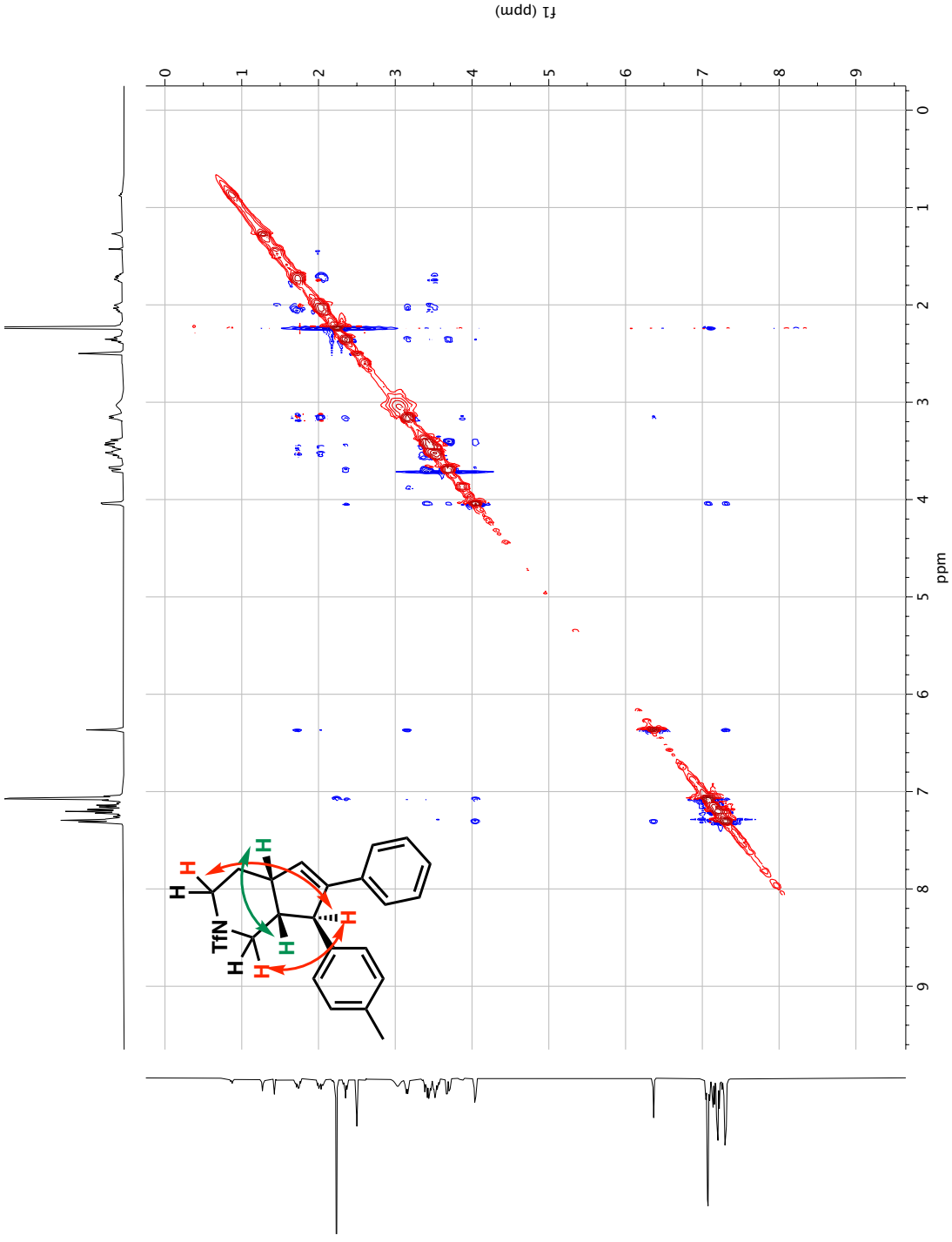


^{13}C NMR (101 MHz d_6-DMSO, 90 ºC) of **213a**.

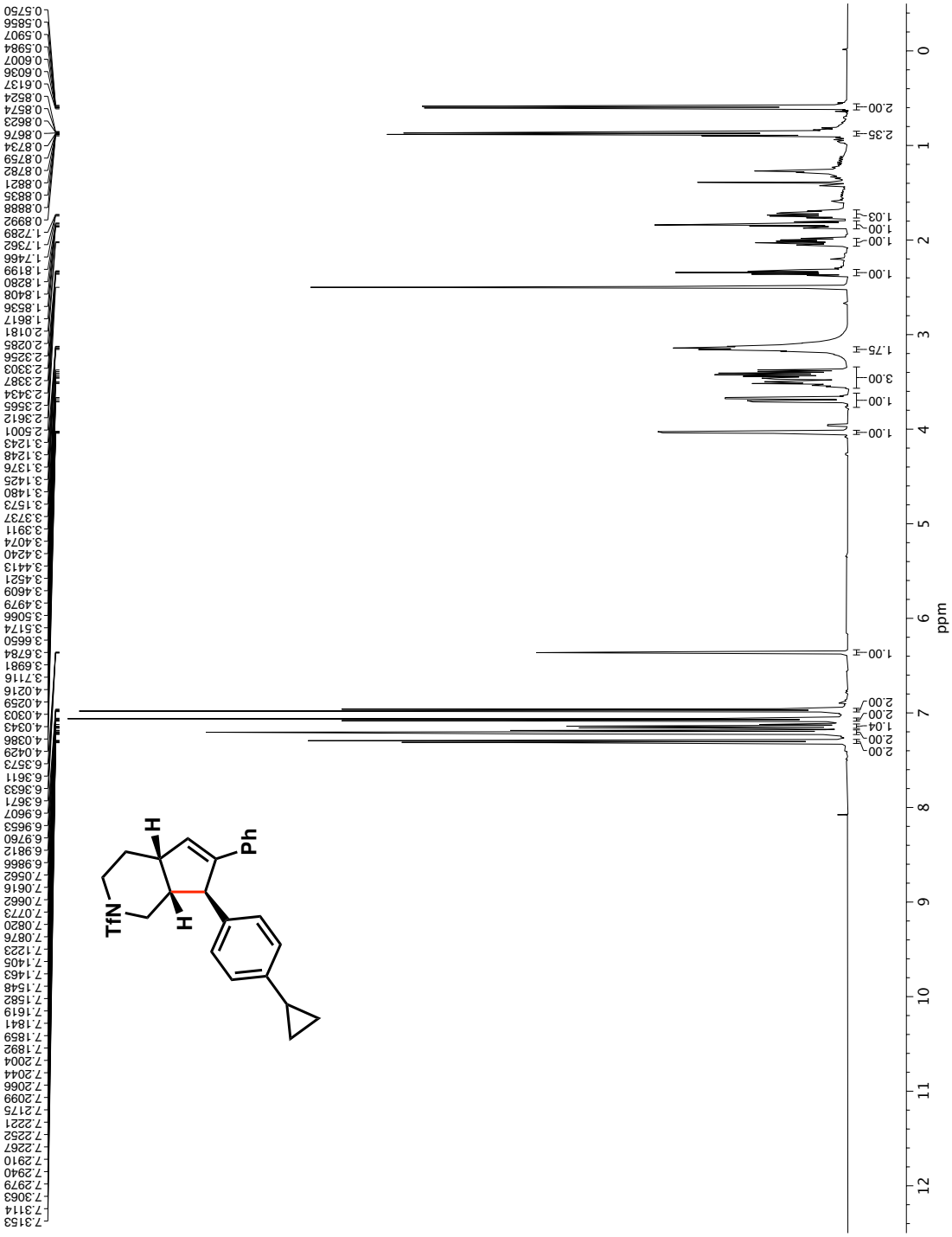
^{19}F NMR (376 MHz, d_6-DMSO, 90 ºC) of **213a**.



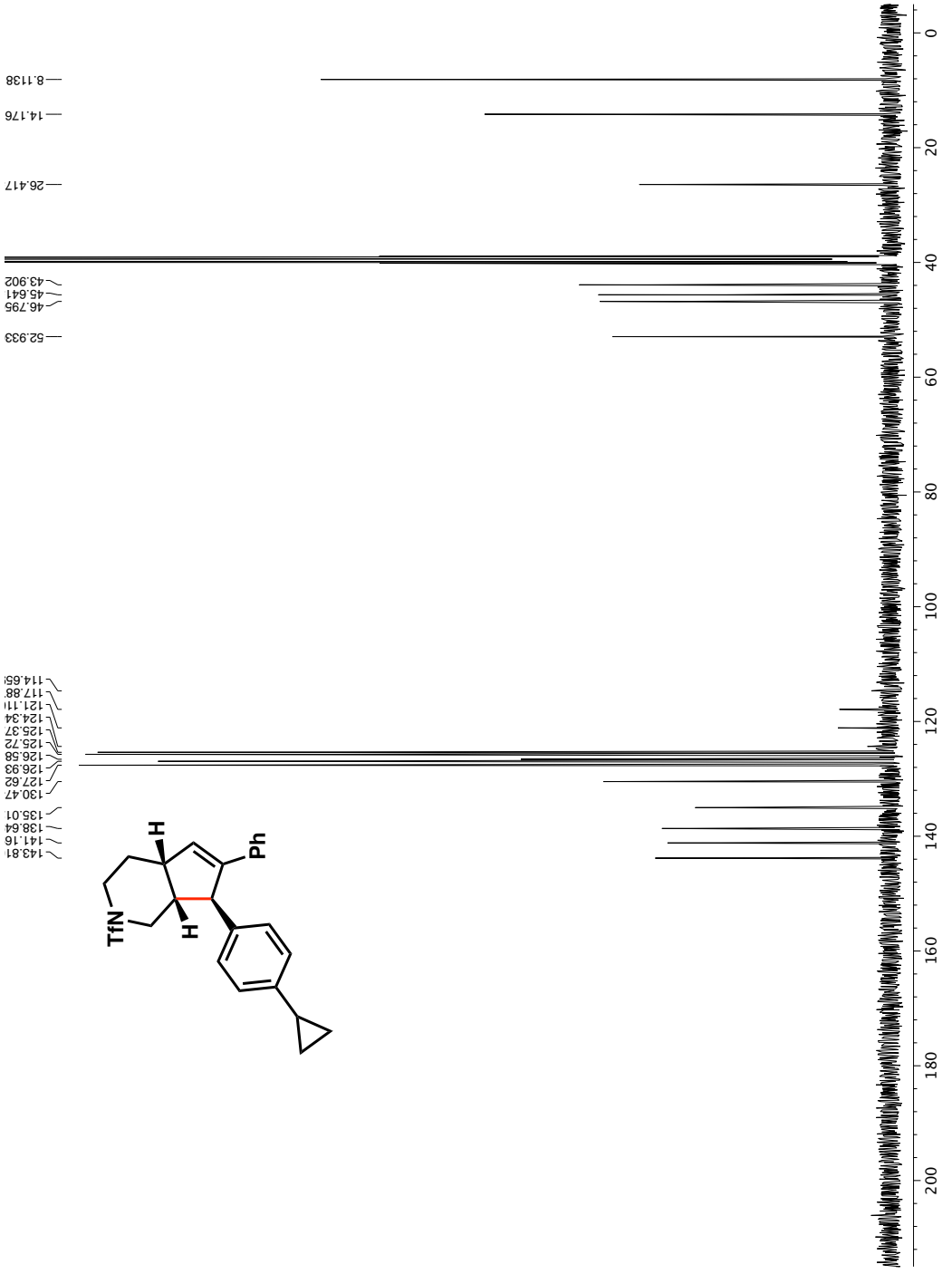
COSY NMR (400 MHz, d_6-DMSO, 90 °C) of **213a.**



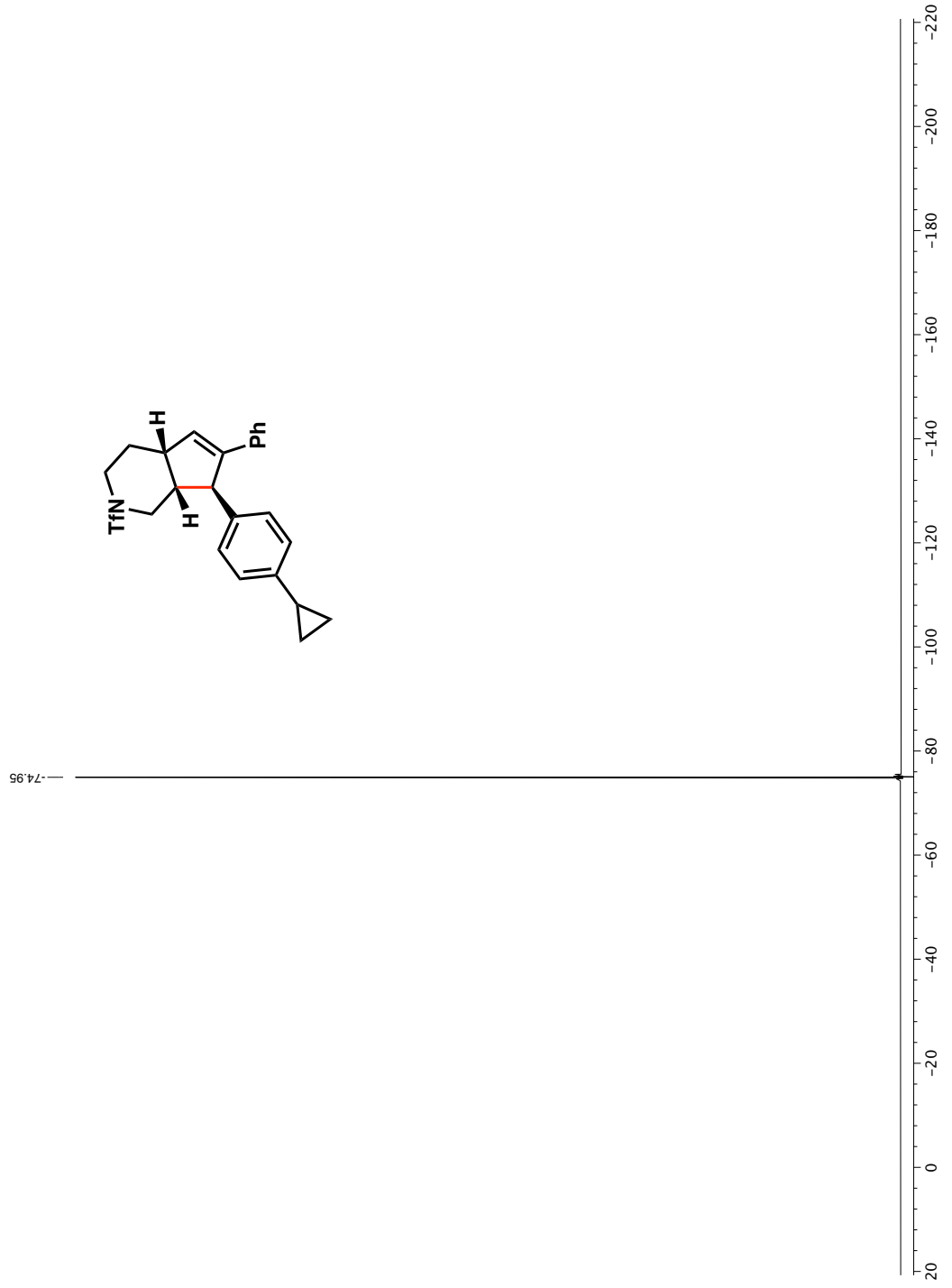
NOESY NMR (400 MHz, d_6-DMSO, 90 ºC) of **213a**.



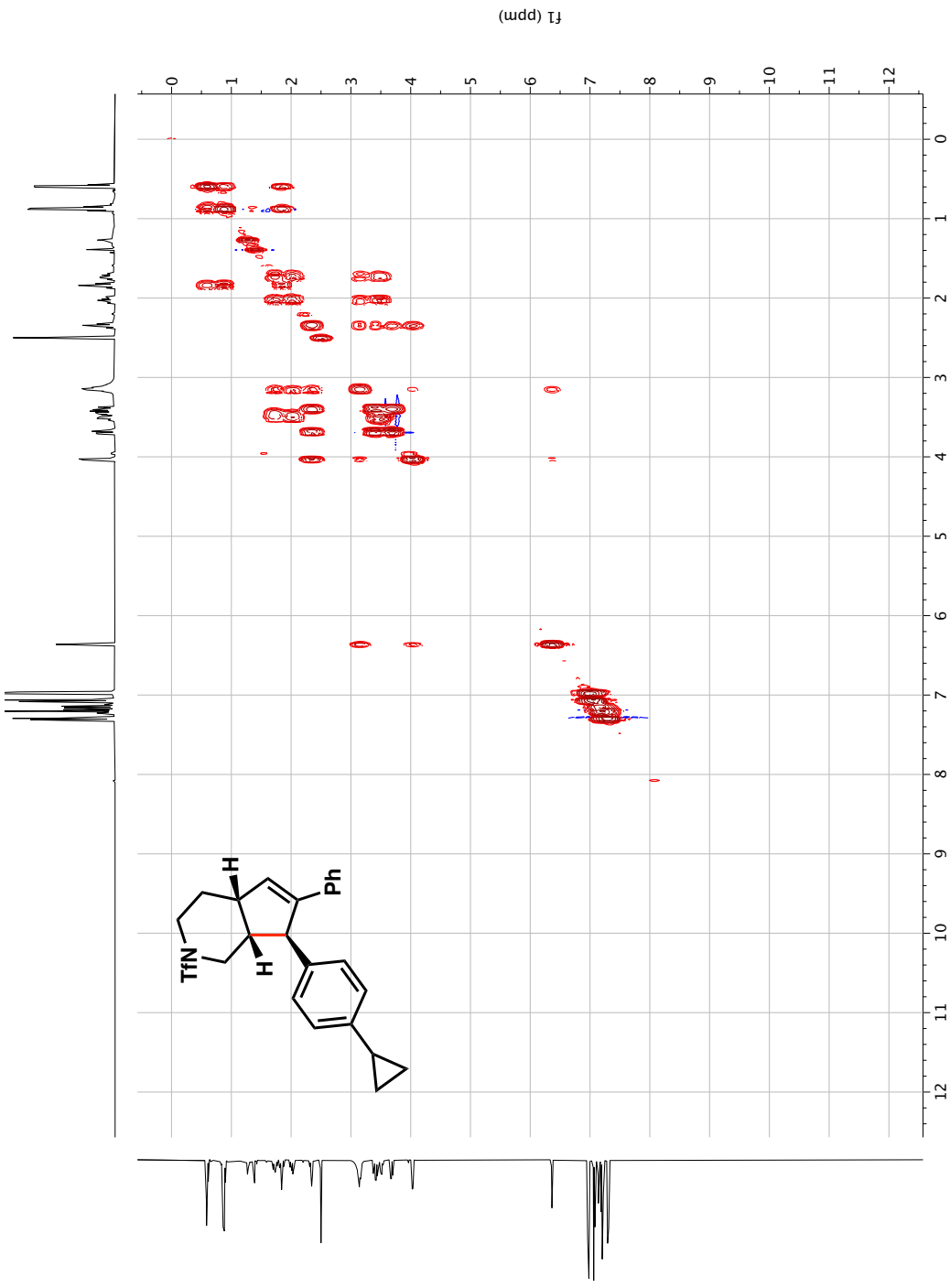
^{1}H NMR (400 MHz d_6-DMSO, 90 °C) of **213b.**



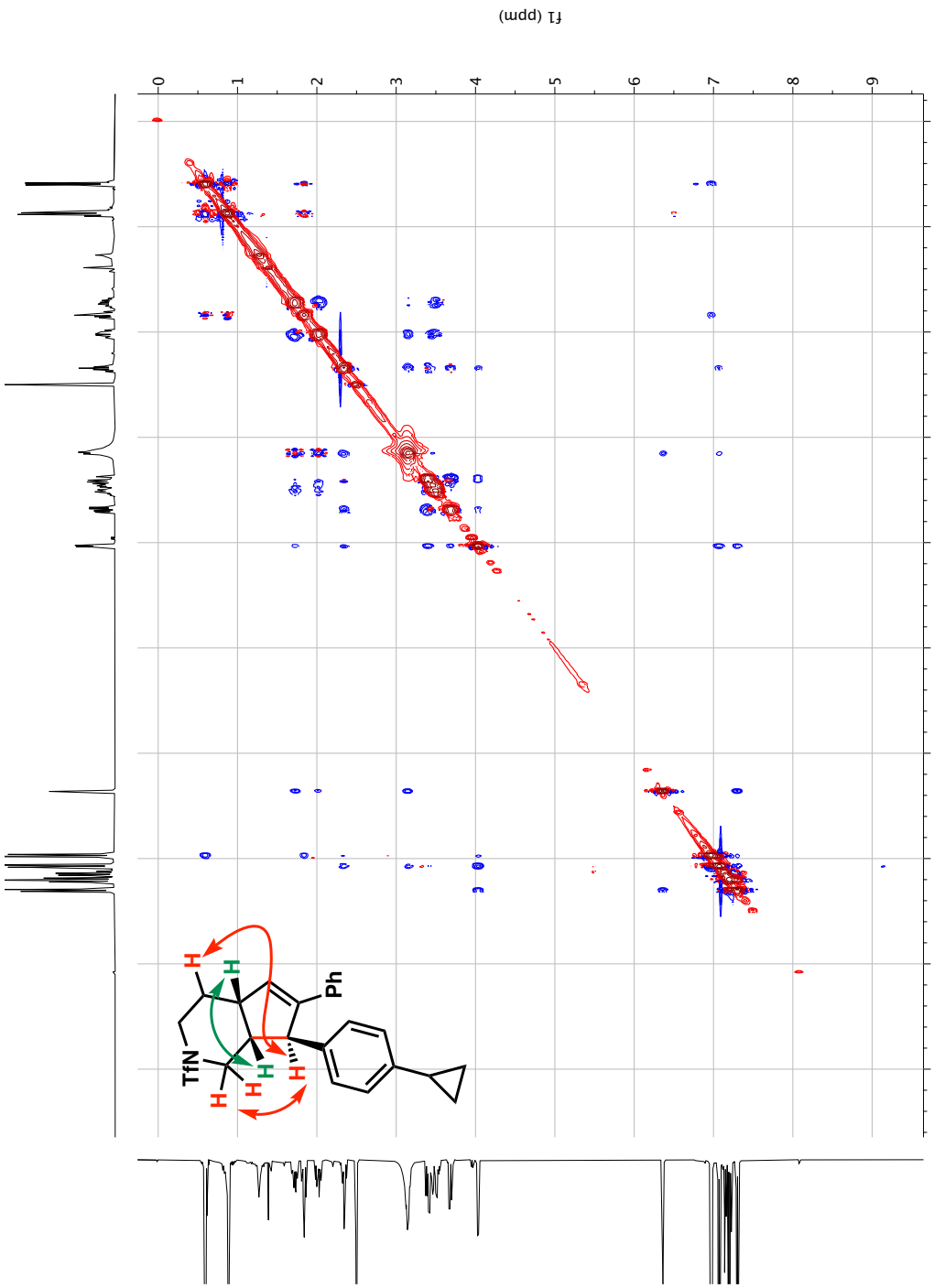
^{13}C NMR (101 MHz, d_6-DMSO, 90 ºC) of **213b**.



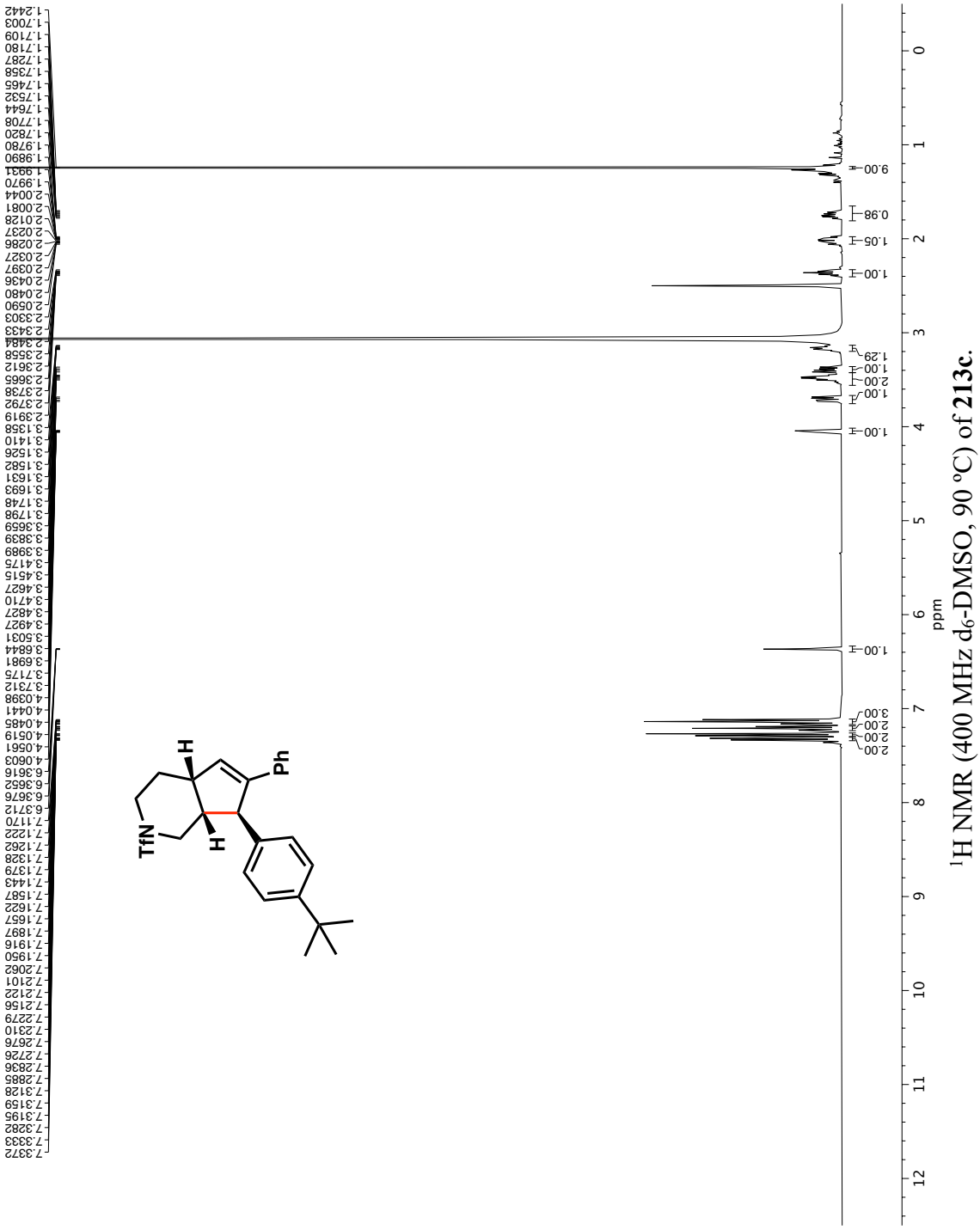
^{19}F NMR (376 MHz, d_6-DMSO, 90 ºC) of **213b**.



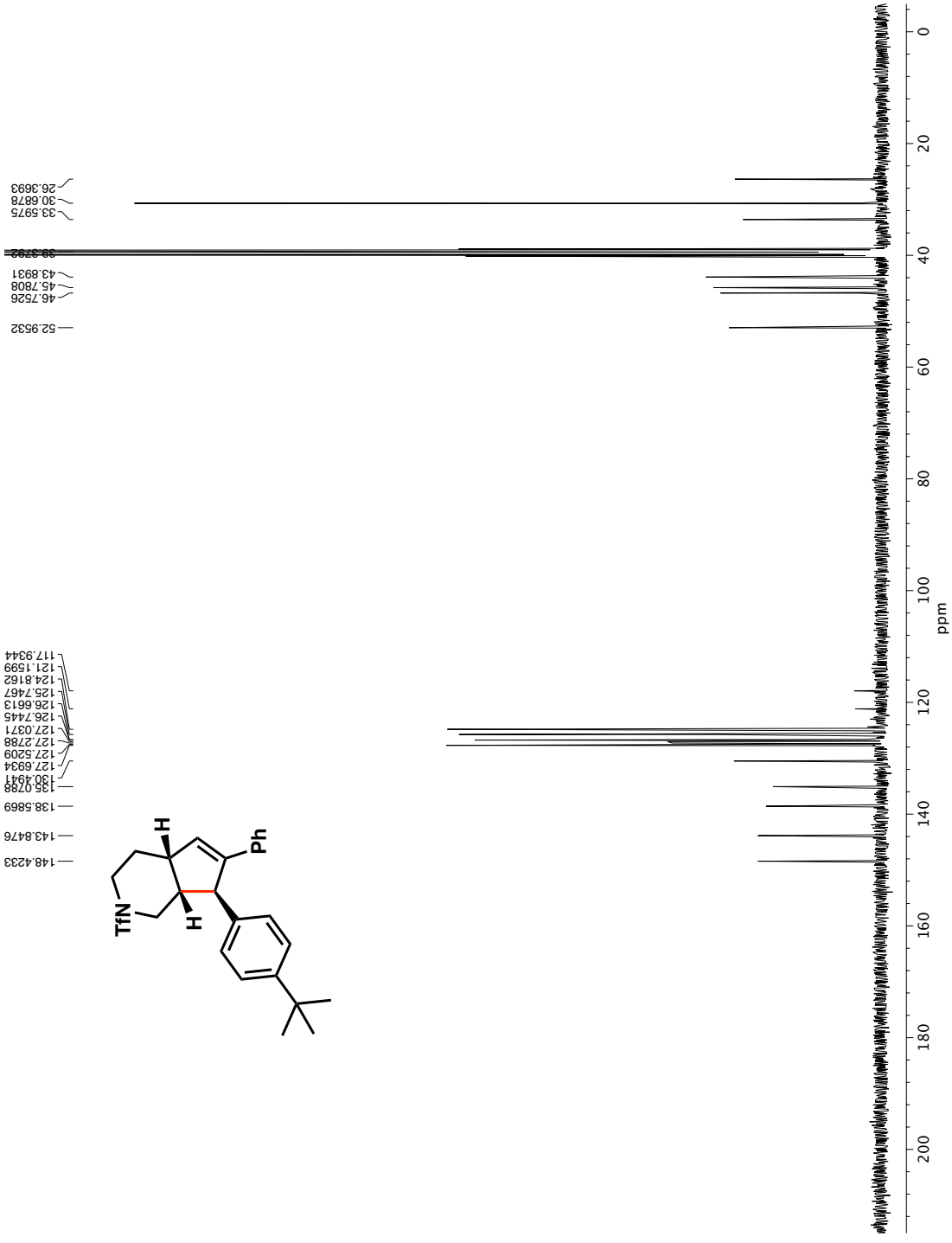
COSY NMR (400 MHz, d_6-DMSO, 90 °C) of **213b**.



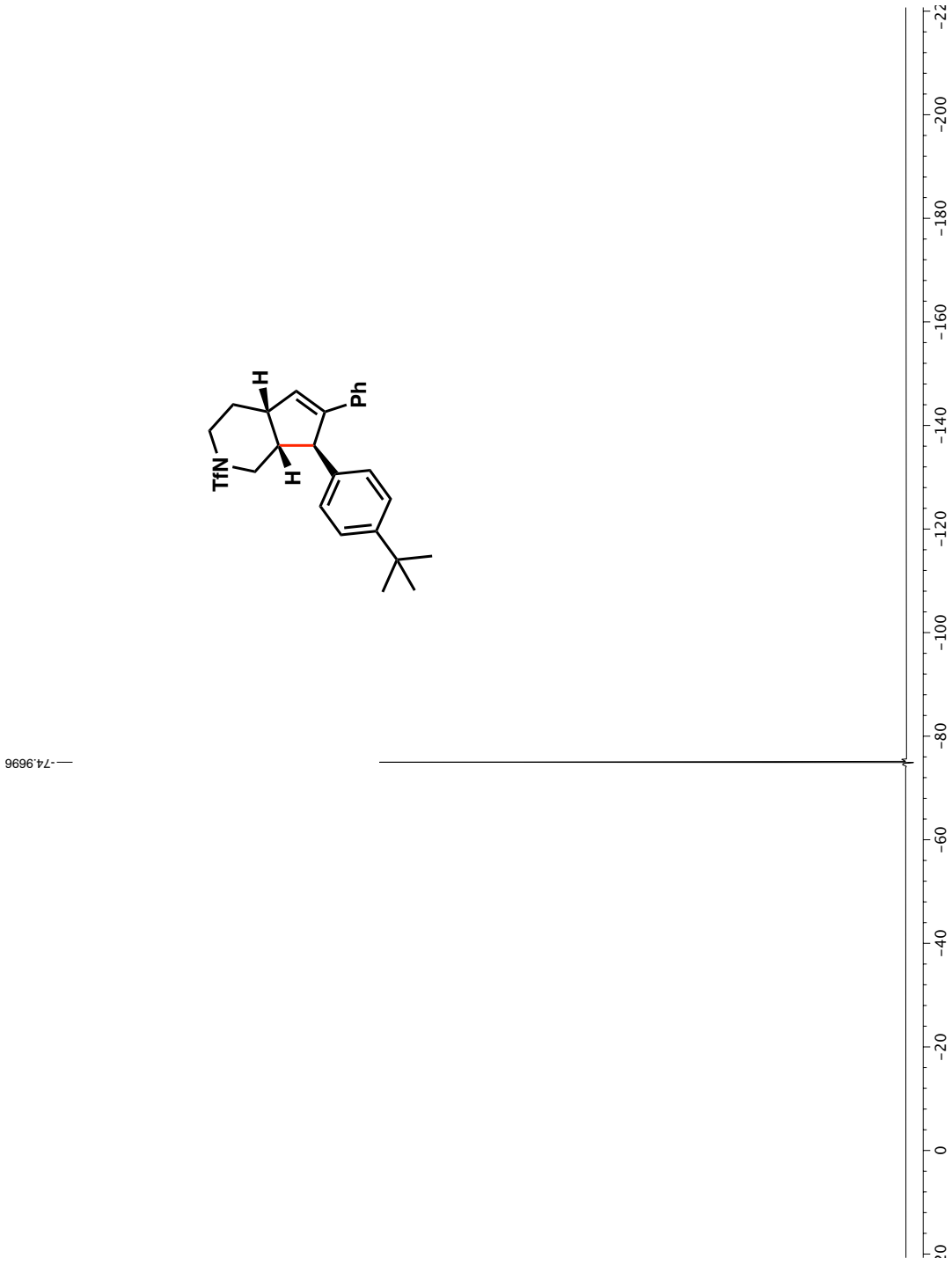
NOESY NMR (400 MHz, d_6-DMSO, 90 °C) of **213b**.



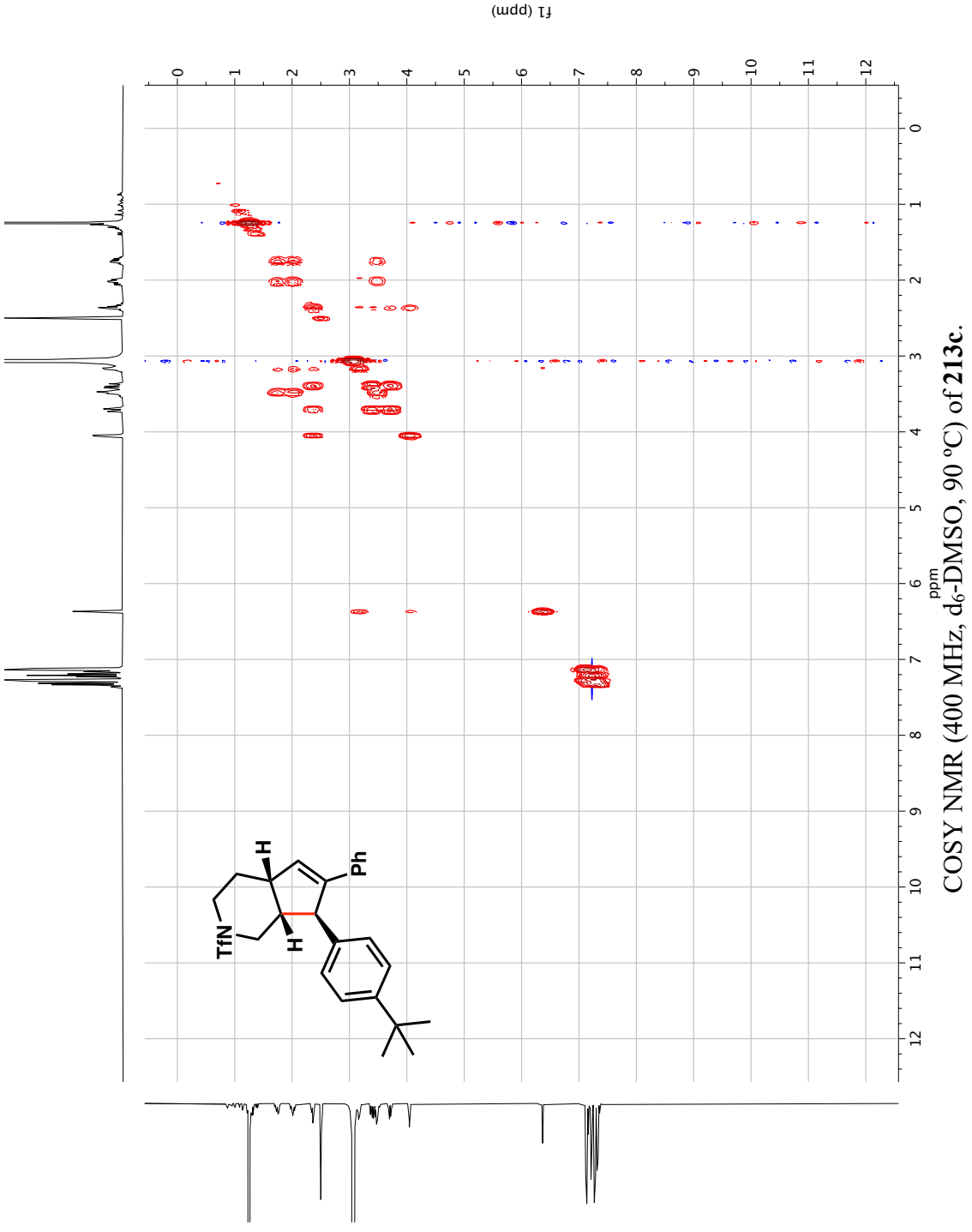
^{1}H NMR (400 MHz d_6-DMSO, 90 ºC) of **213c**.



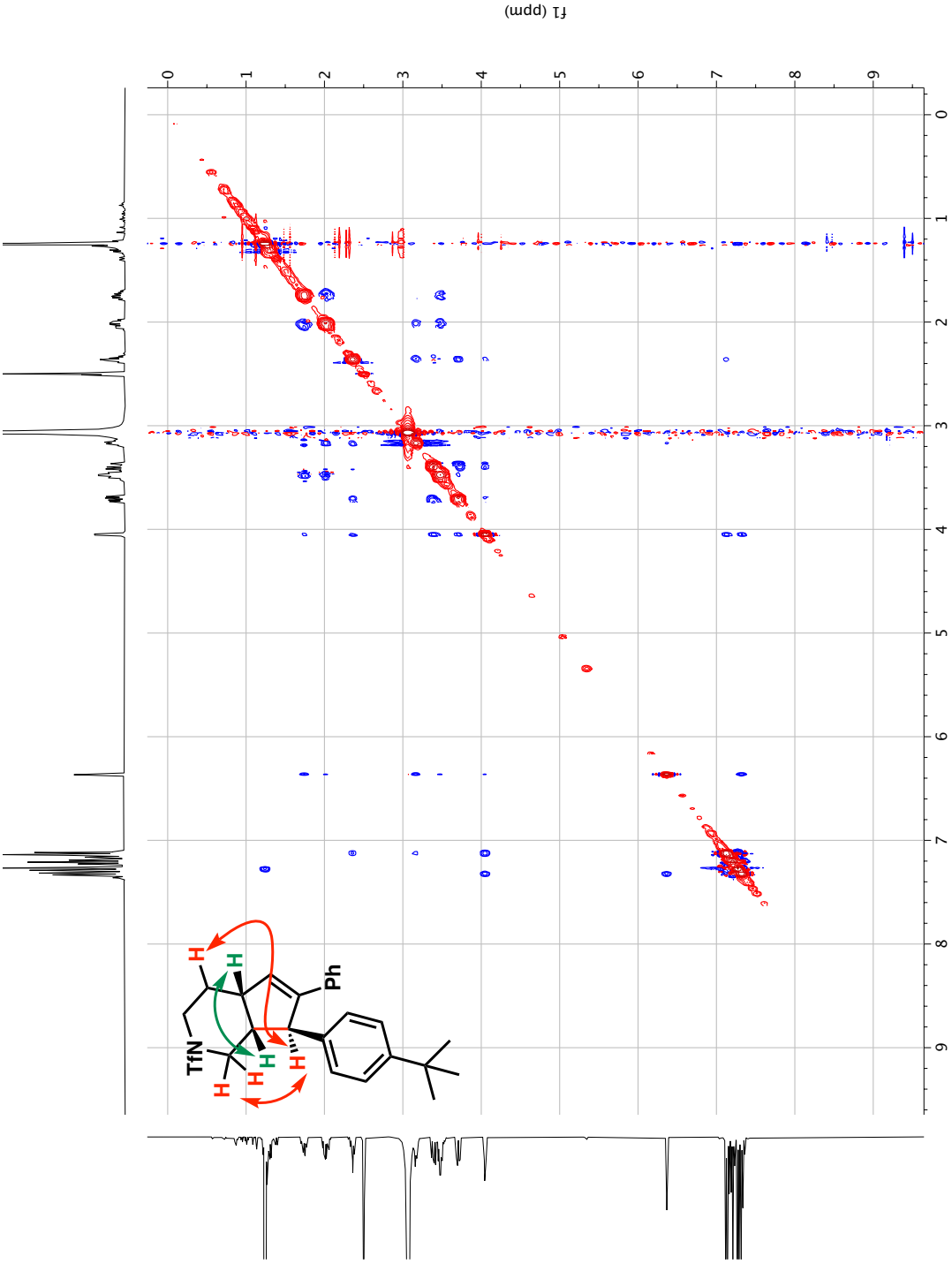
^{13}C NMR (101 MHz, d_6-DMSO, 90 °C) of **213c**.



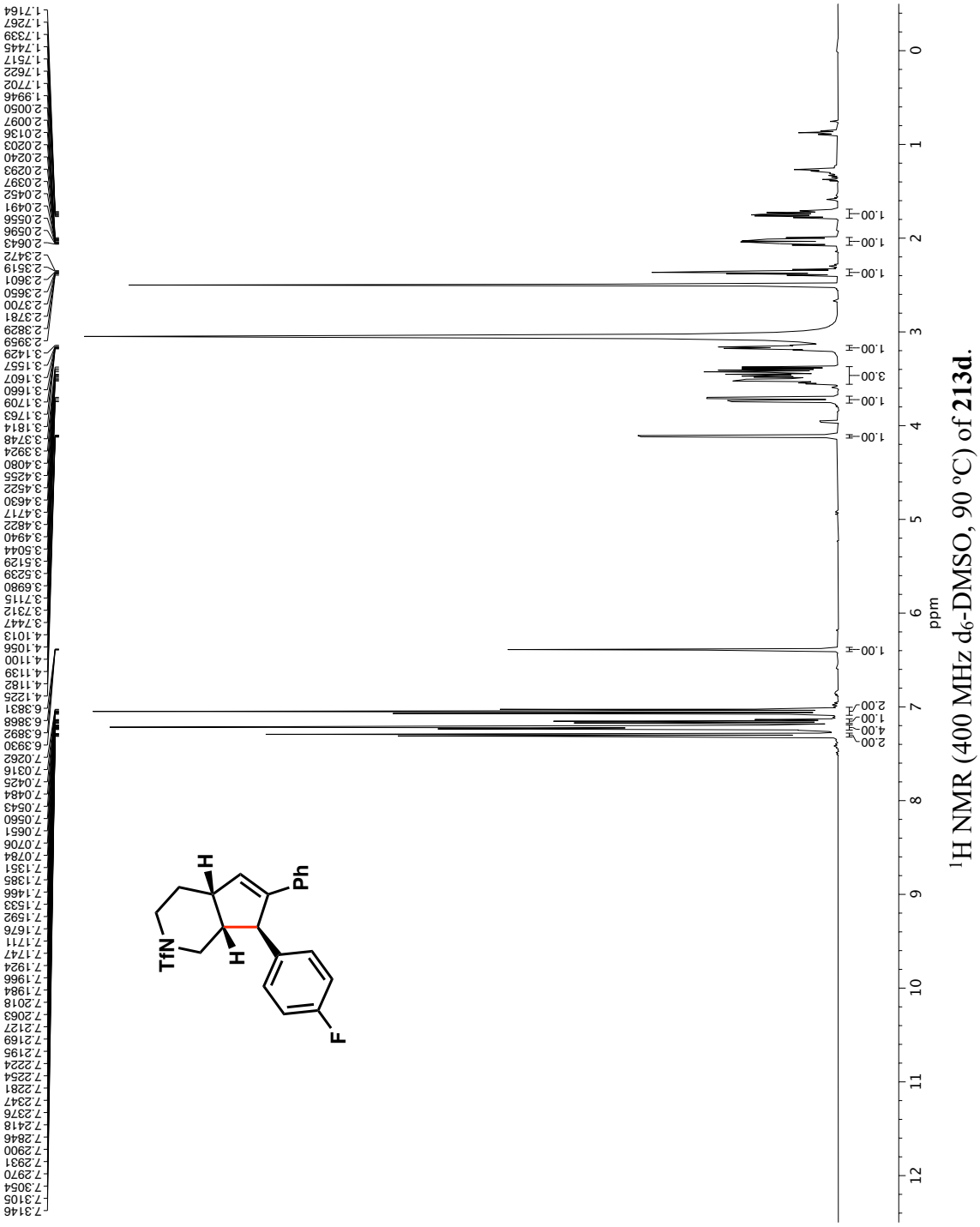
^{19}F NMR (376 MHz, d_6-DMSO, 90 ºC) of **213c**.



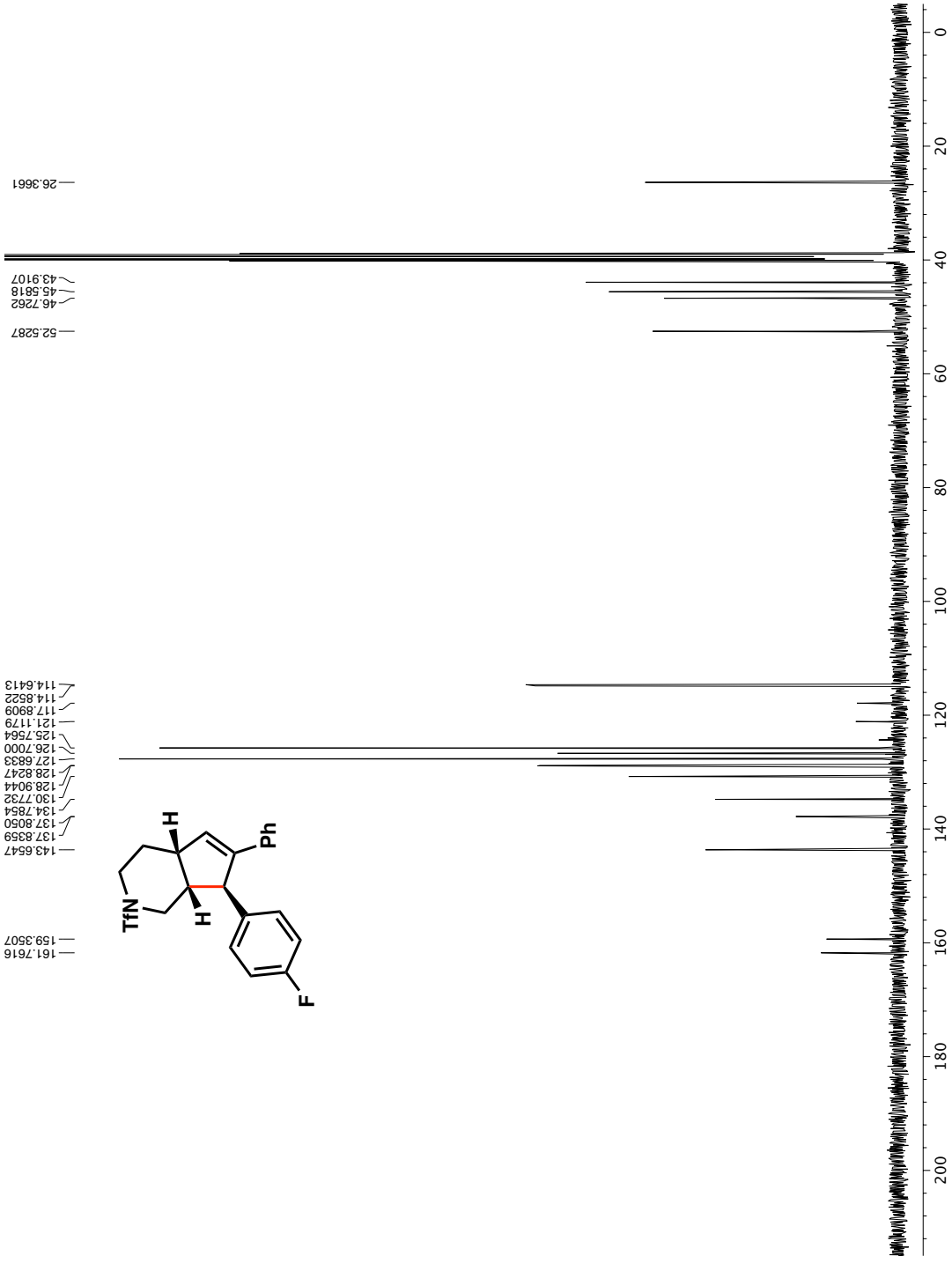
COSY NMR (400 MHz, d_6-DMSO, 90 ºC) of **213c**.



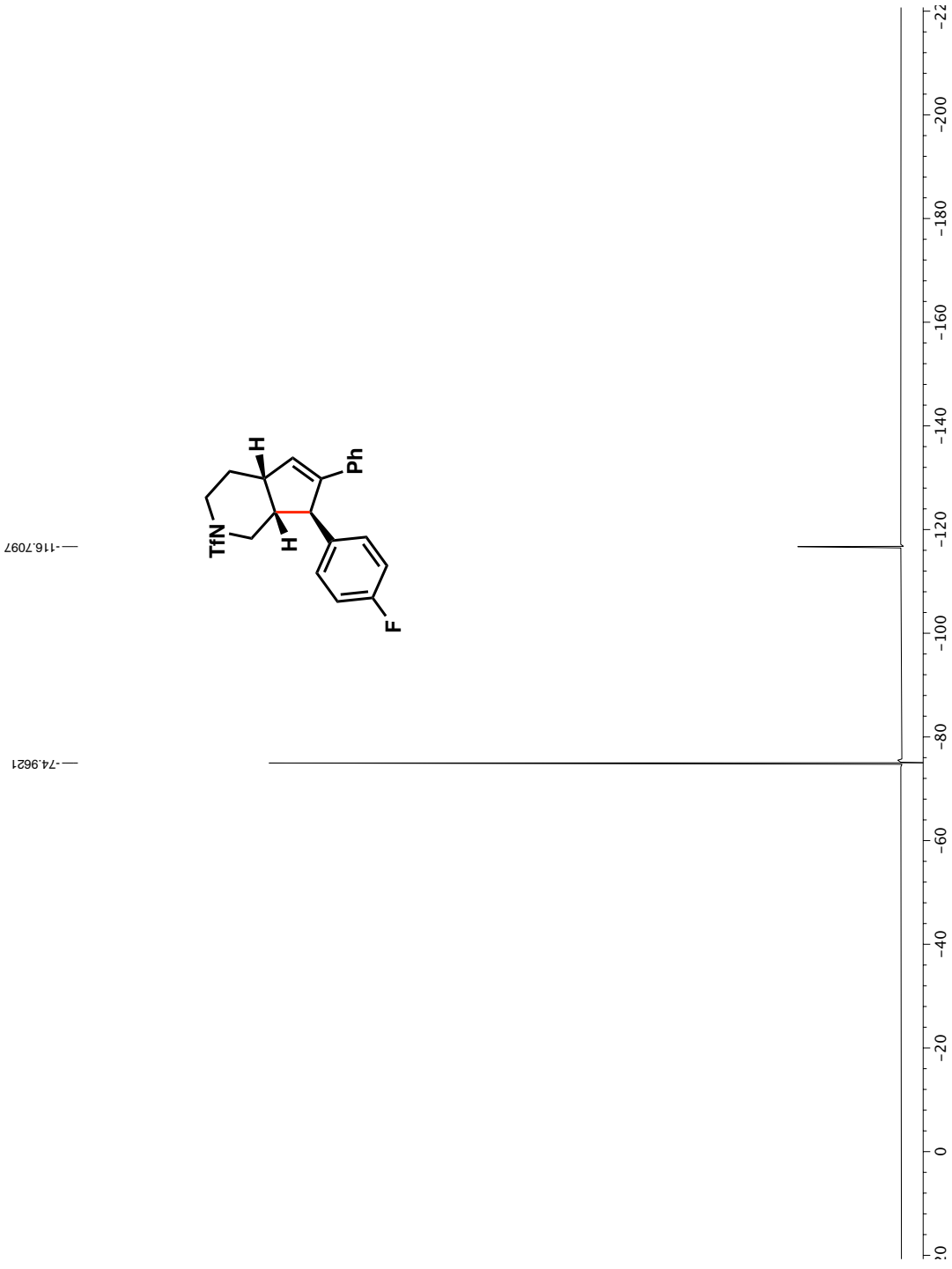
NOESY NMR (400 MHz, d_6-DMSO, 90 °C) of **213c**.



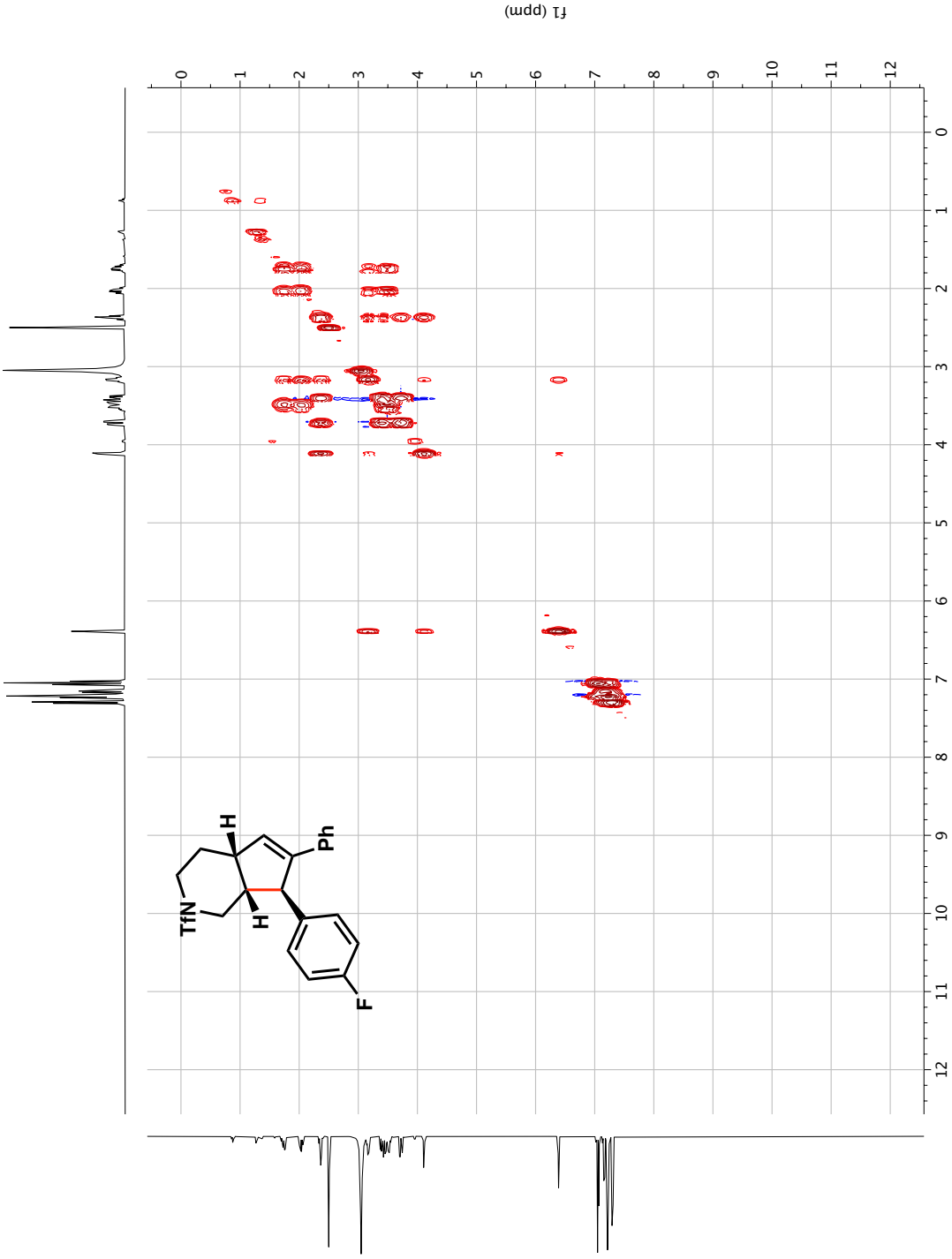
^{1}H NMR (400 MHz d_6-DMSO, 90 °C) of **213d**.



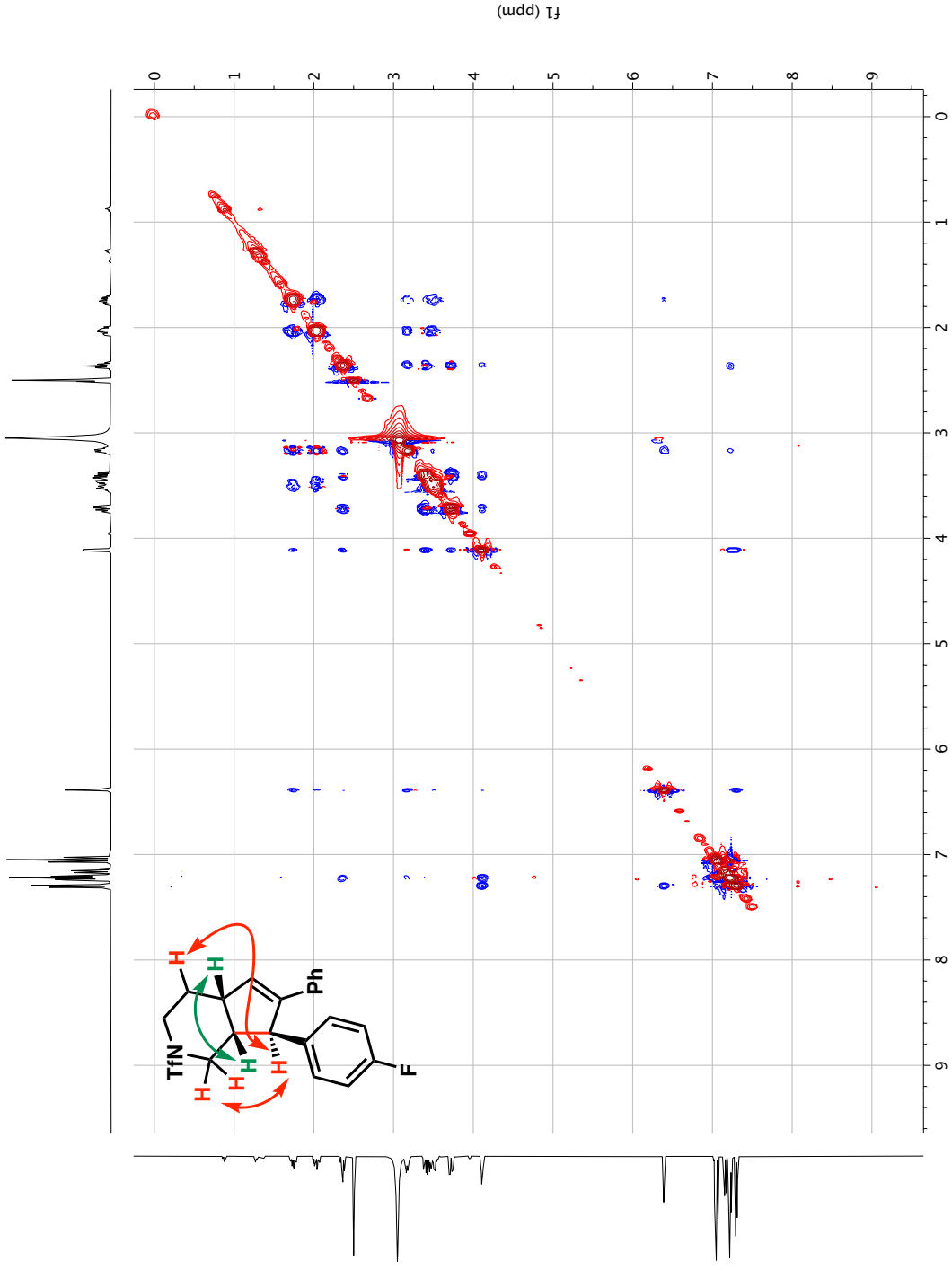
^{13}C NMR (101 MHz, d_6-DMSO, 90 ºC) of **213d**.



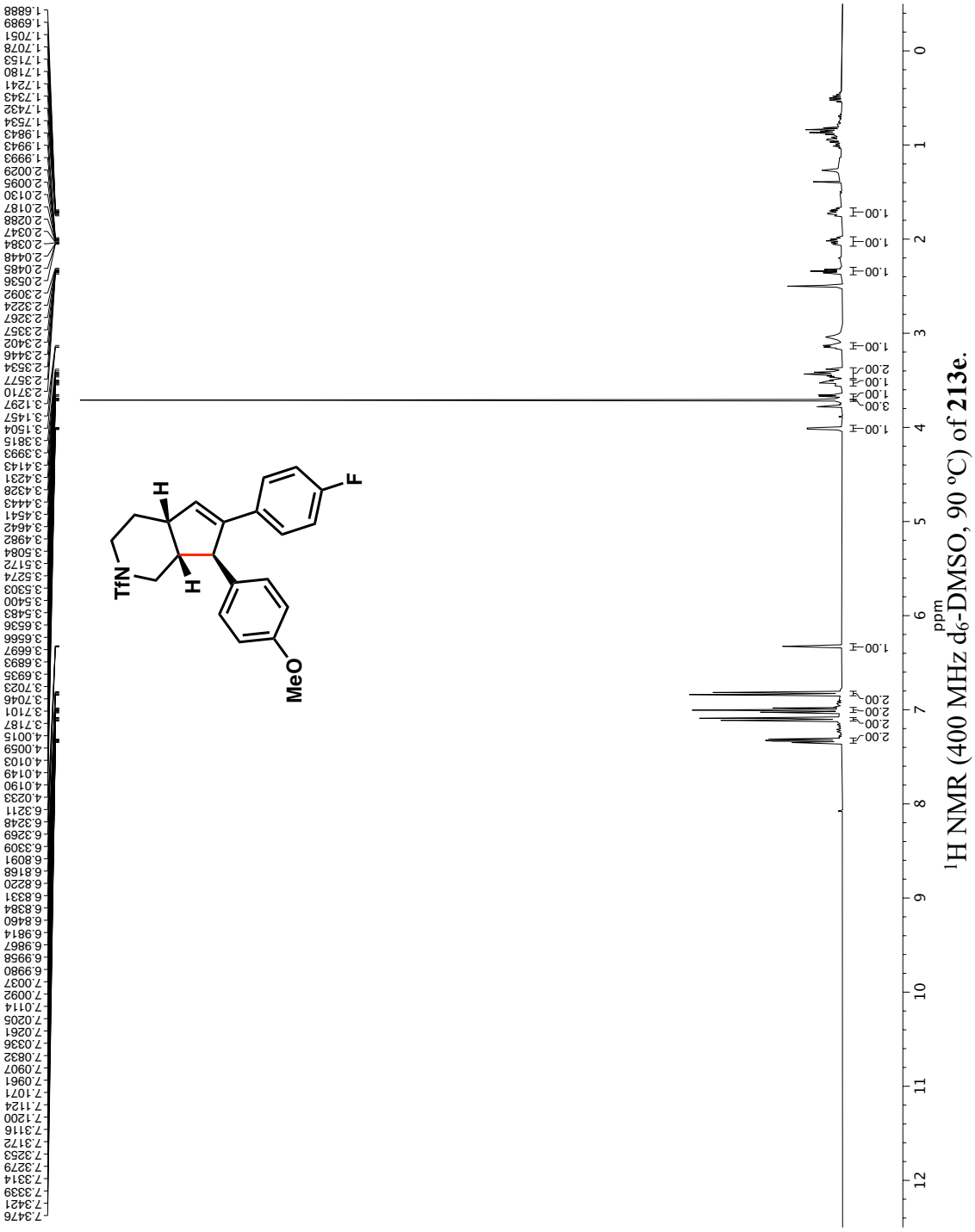
^{19}F NMR (376 MHz, d_6-DMSO, 90 °C) of **213d**.



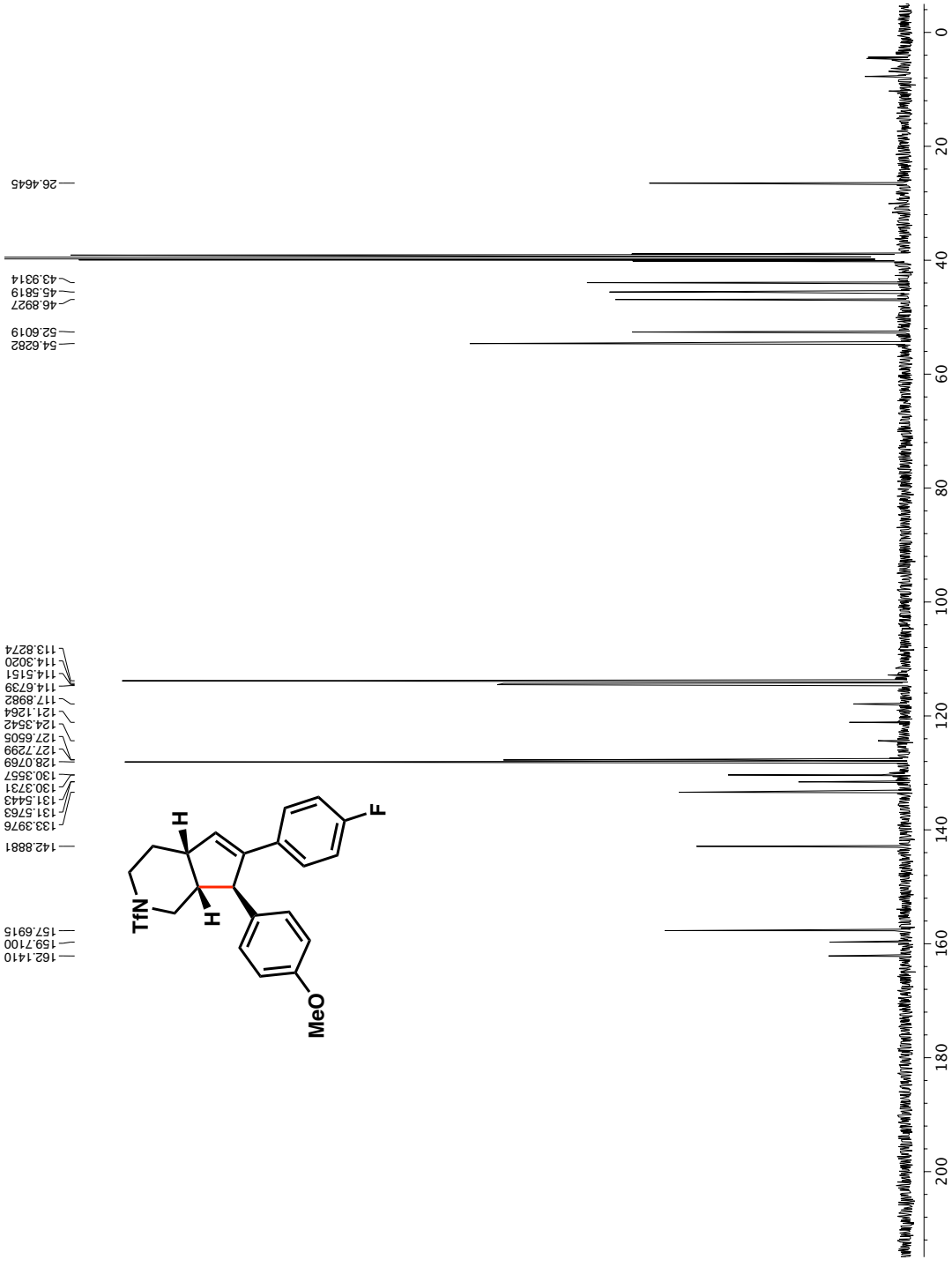
COSY NMR (400 MHz, d_6-DMSO, 90 °C) of **213d**.



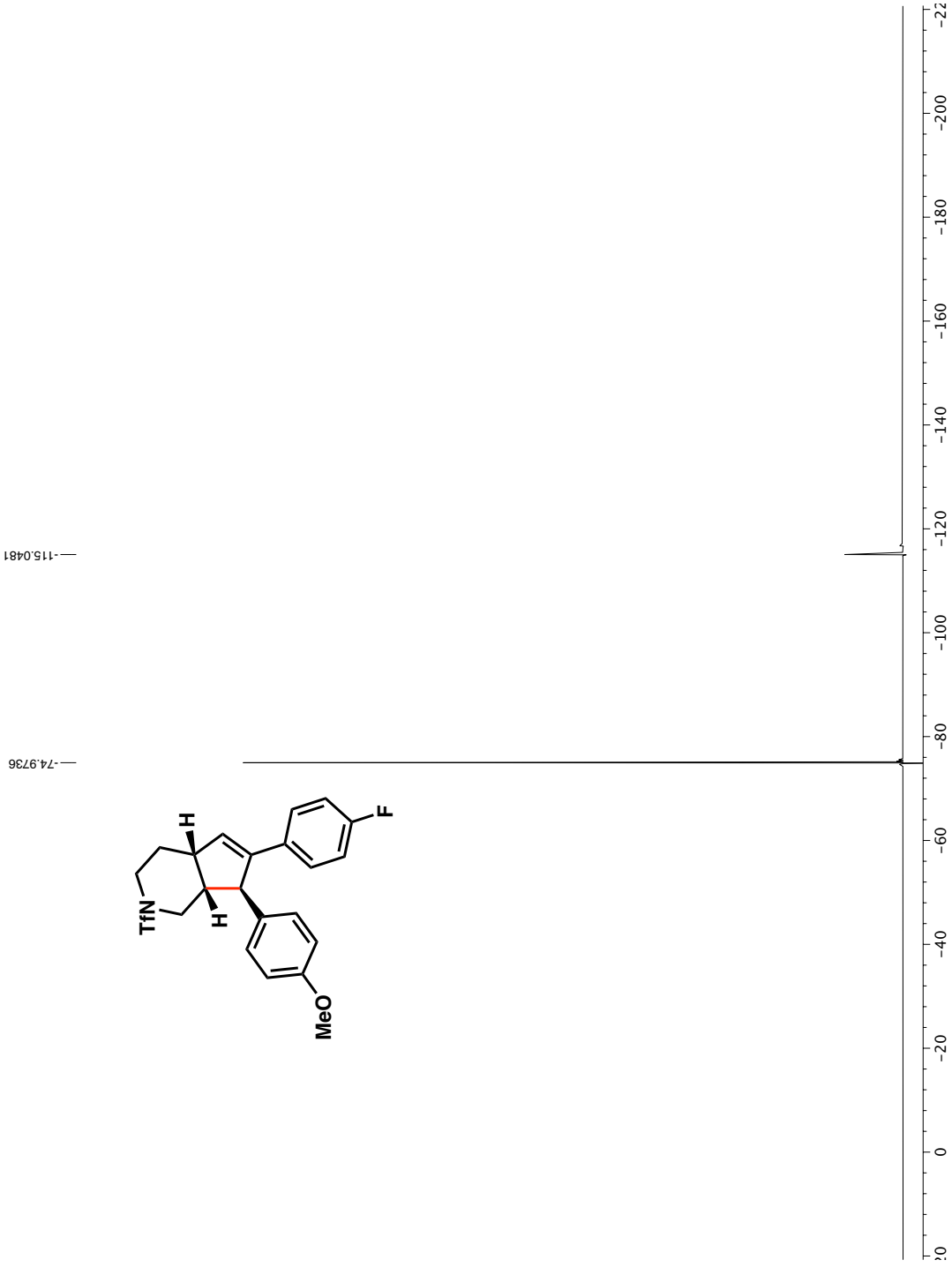
NOESY NMR (400 MHz, d_6-DMSO, 90 °C) of **213d**.



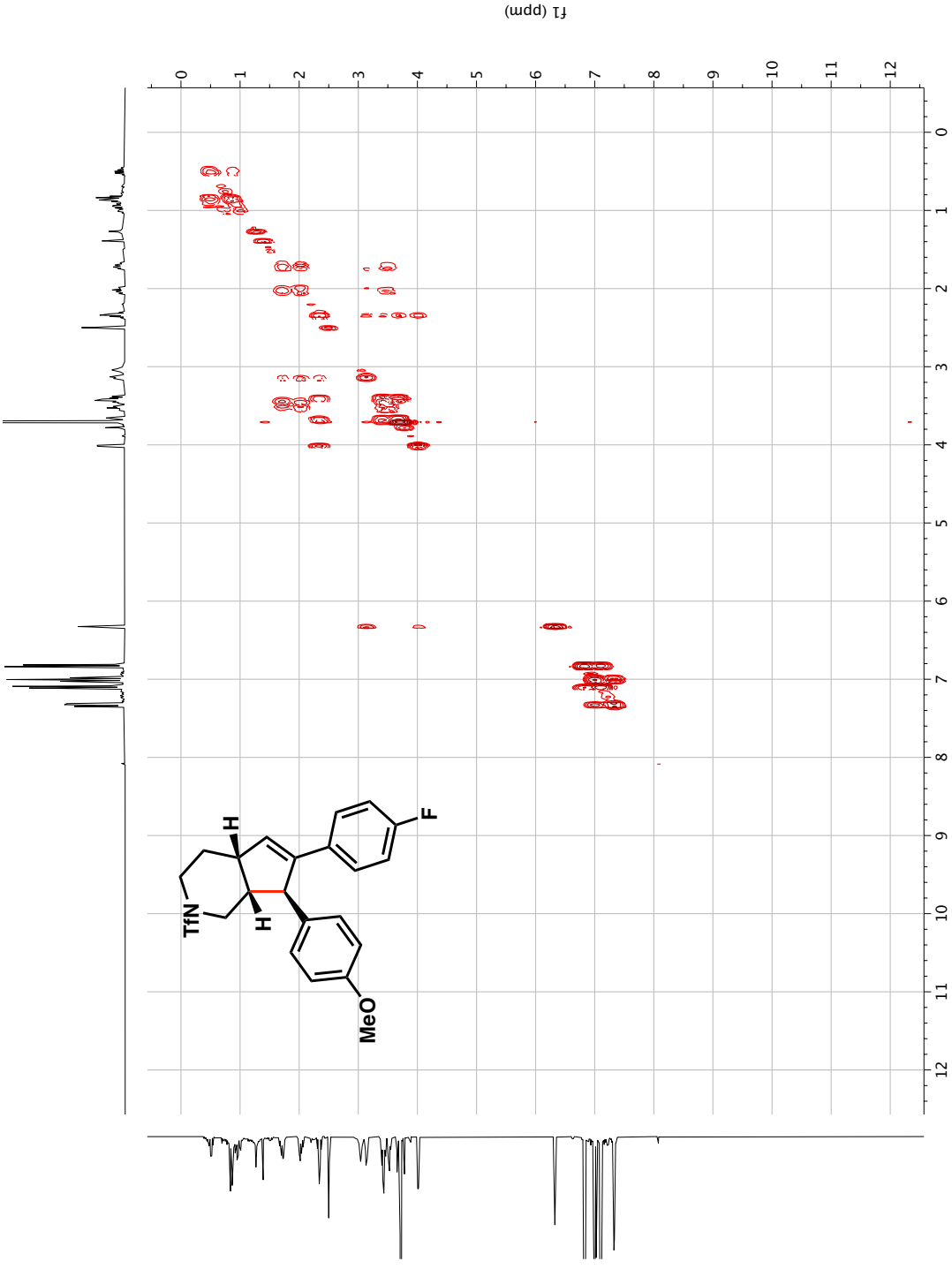
^{1}H NMR (400 MHz d_6-DMSO, 90 °C) of **213e**.



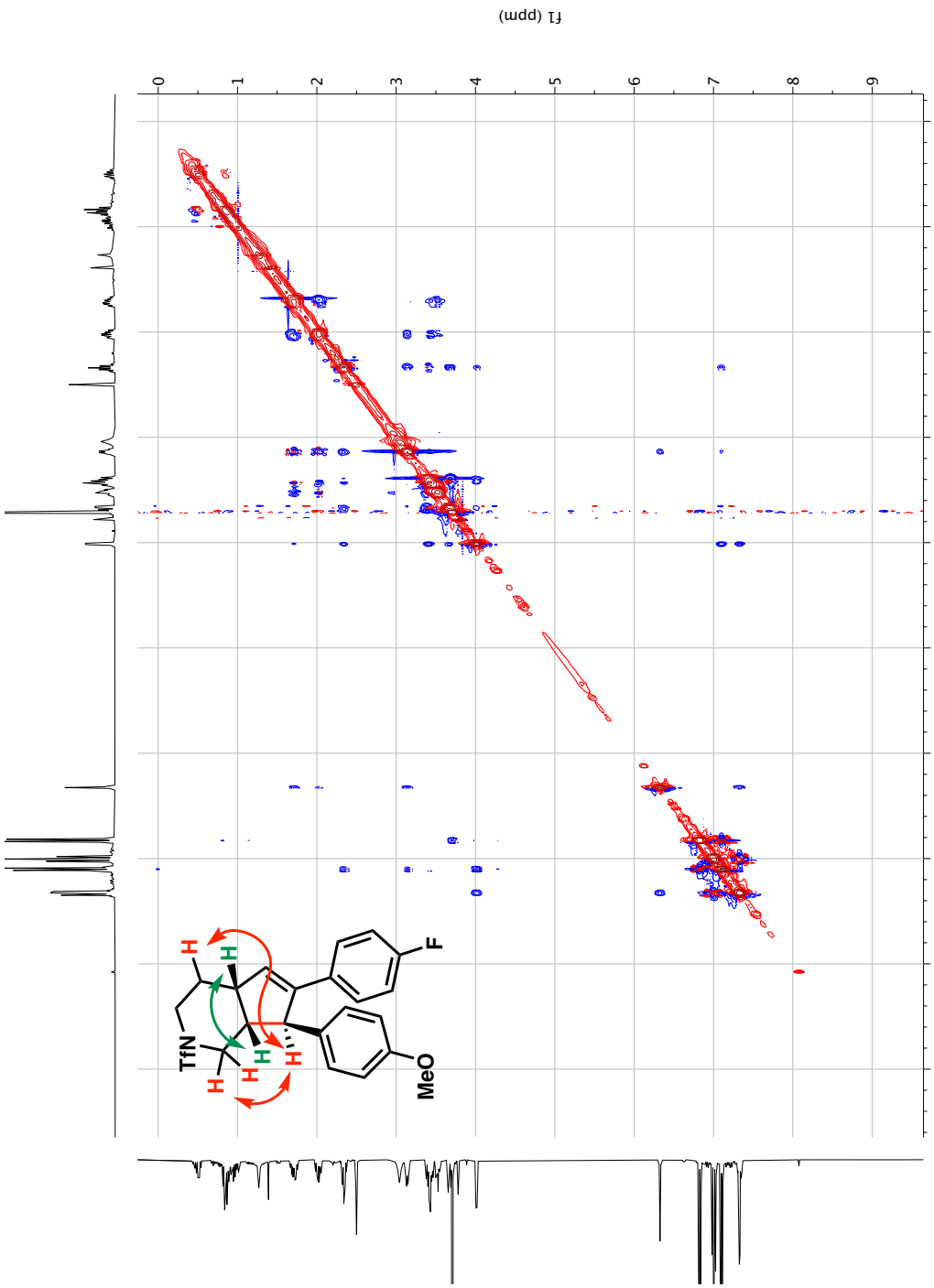
^{13}C NMR (101 MHz, d_6-DMSO, 90 ºC) of **213e**.



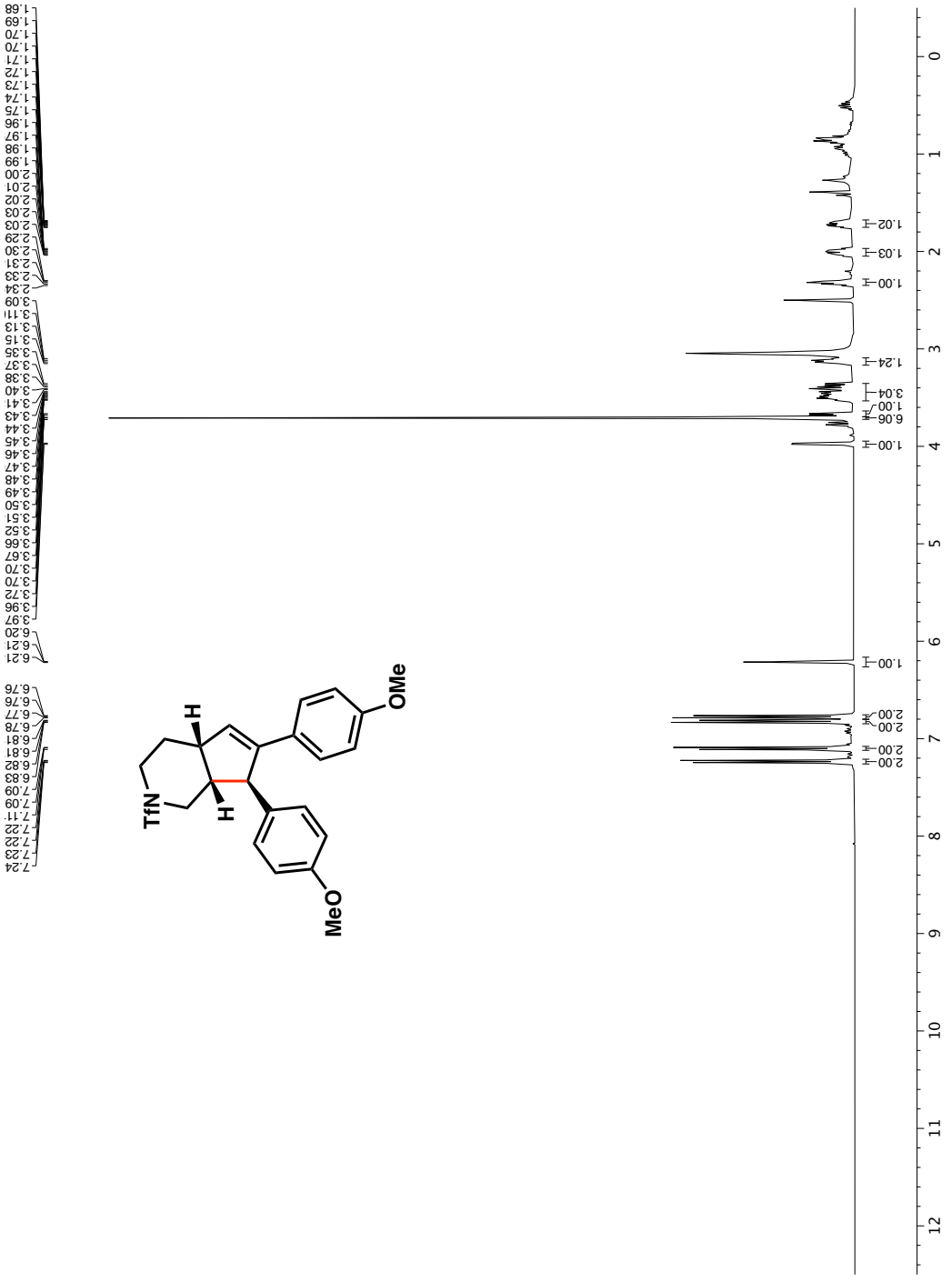
^{19}F NMR (376 MHz, d_6-DMSO, 90 °C) of **213e**.



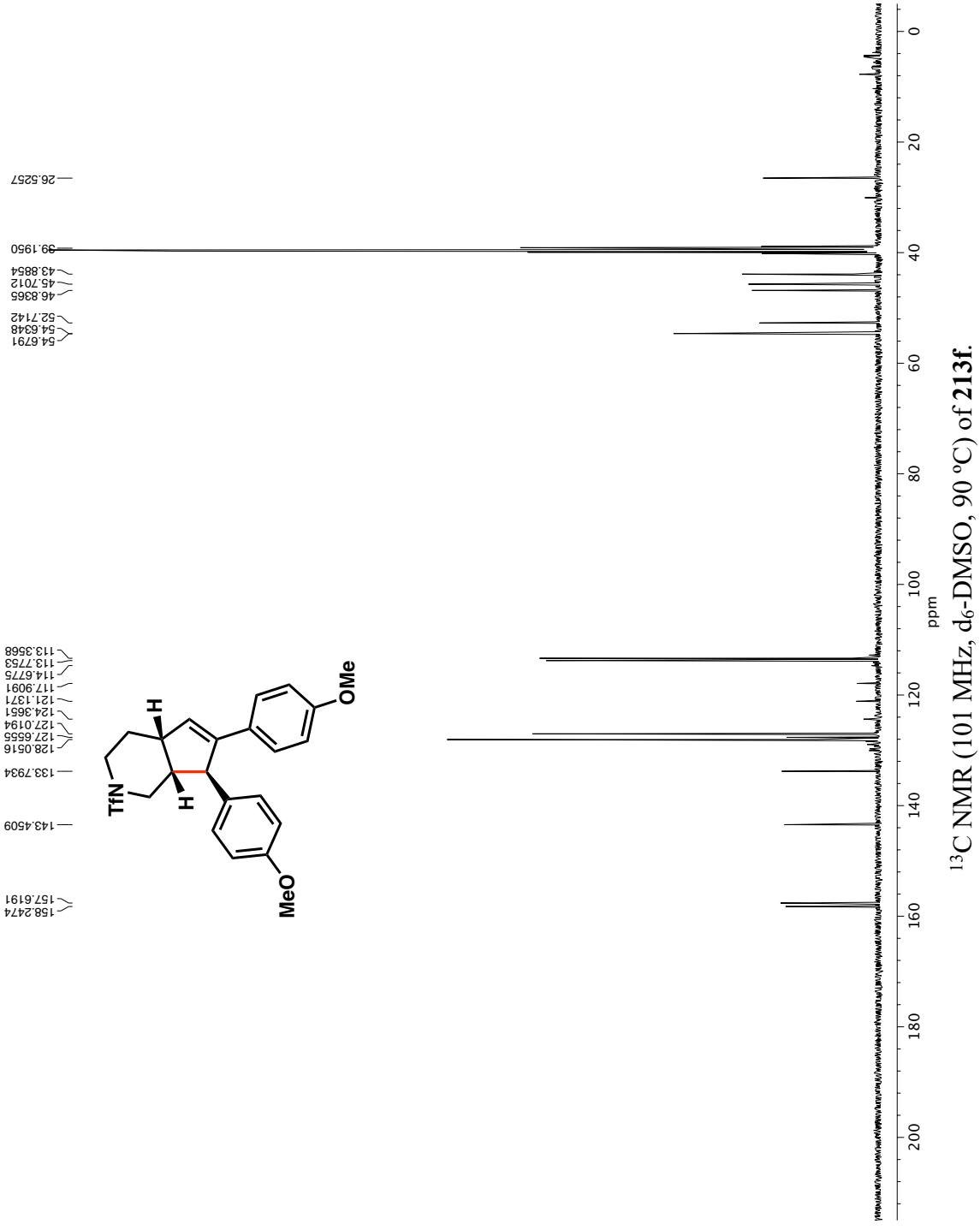
COSY NMR (400 MHz, d_6-DMSO, 90 °C) of **213e**.



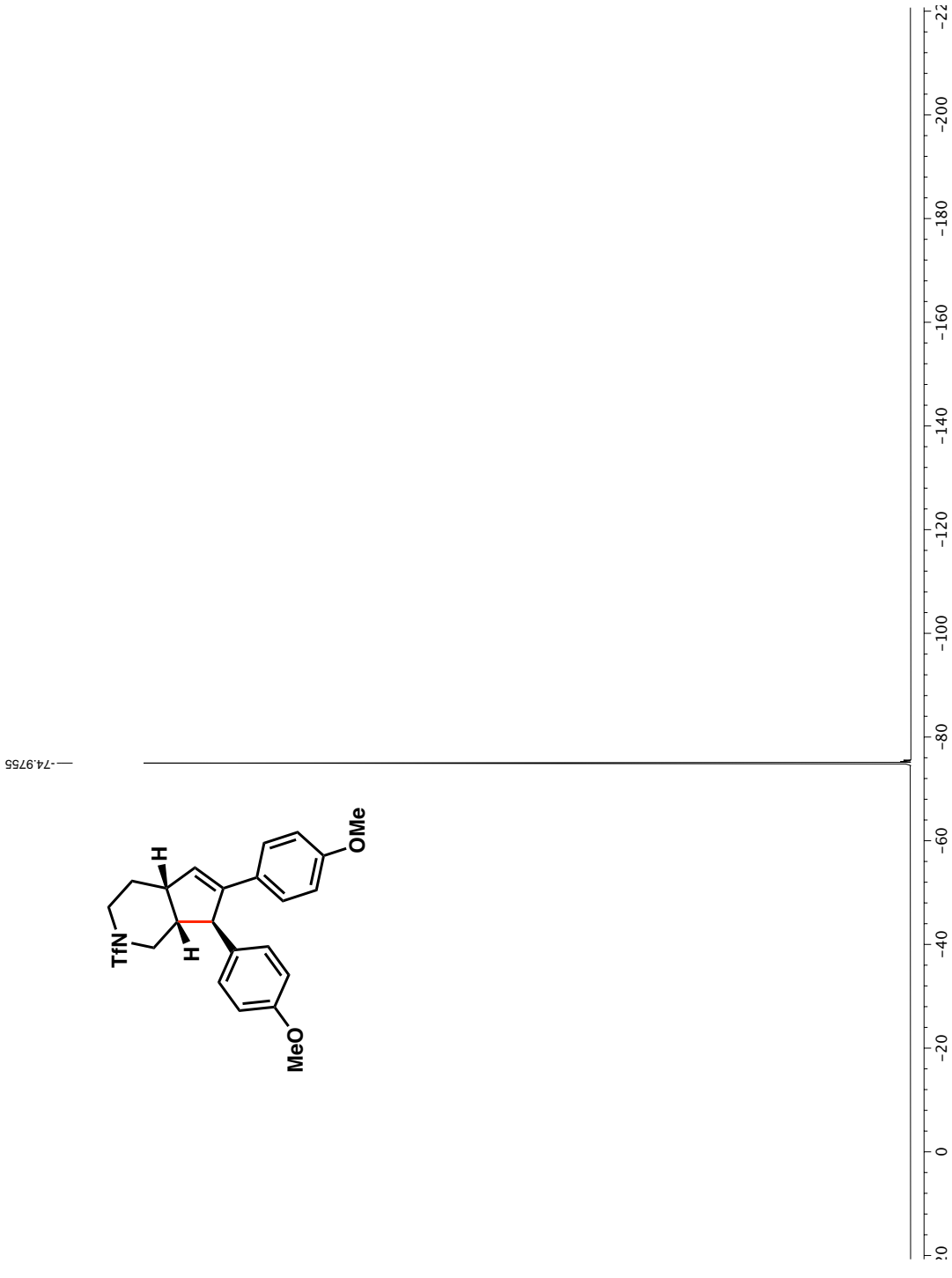
NOESY NMR (400 MHz, d_6-DMSO, 90 °C) of **213e**.



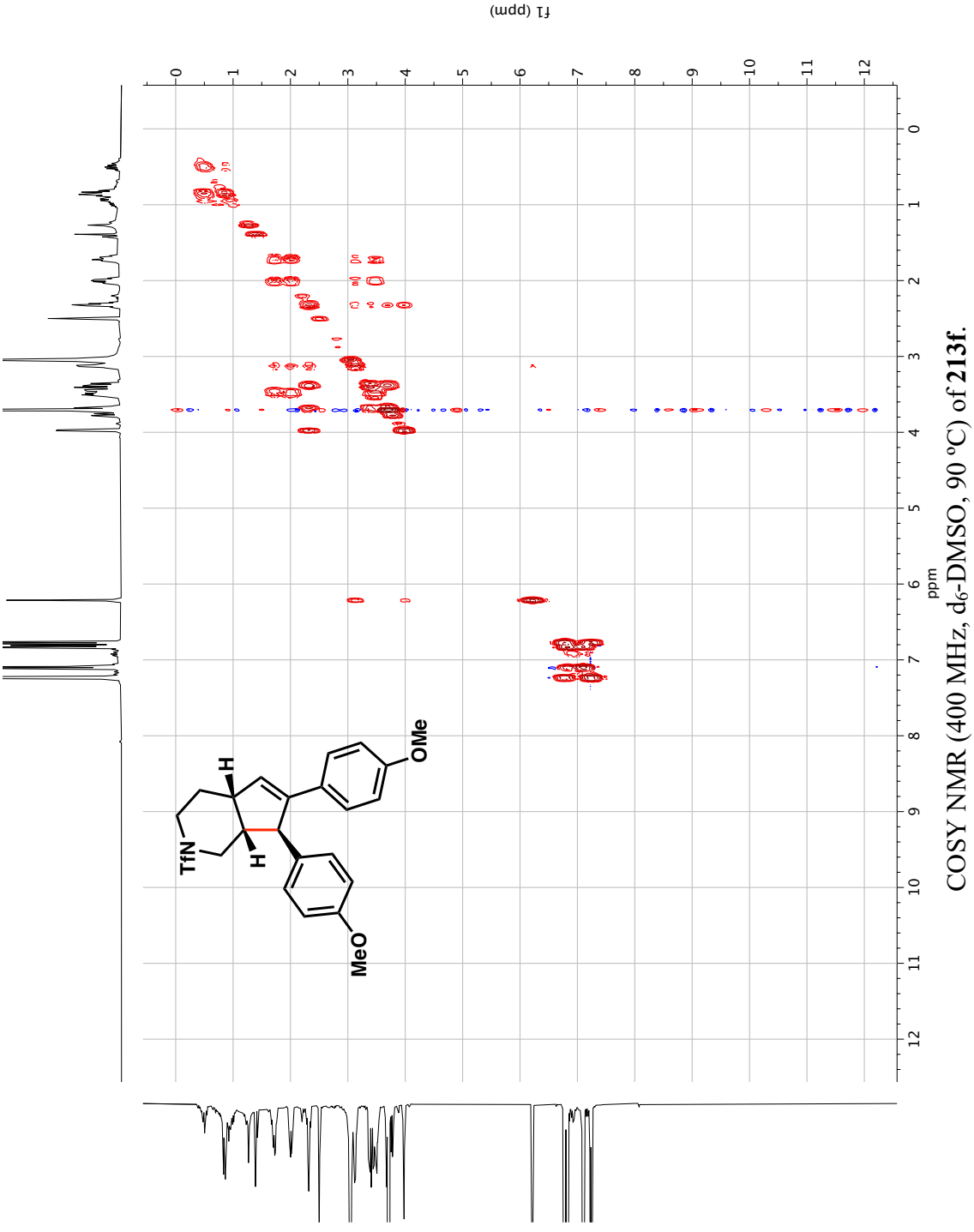
^{1}H NMR (400 MHz d_6-DMSO, 90 ºC) of **213f**.



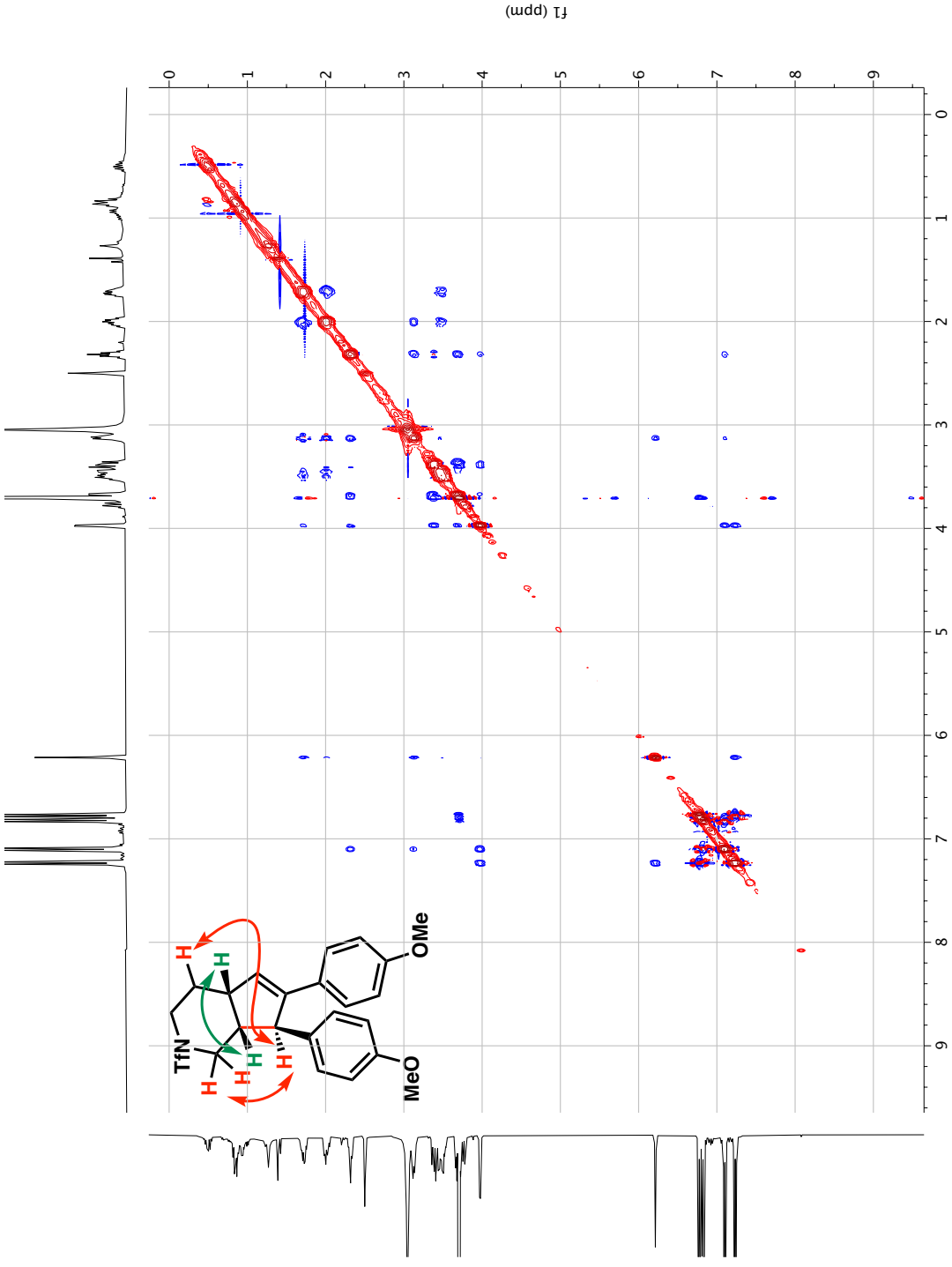
^{13}C NMR (101 MHz, d_6-DMSO, 90 °C) of **213f**.



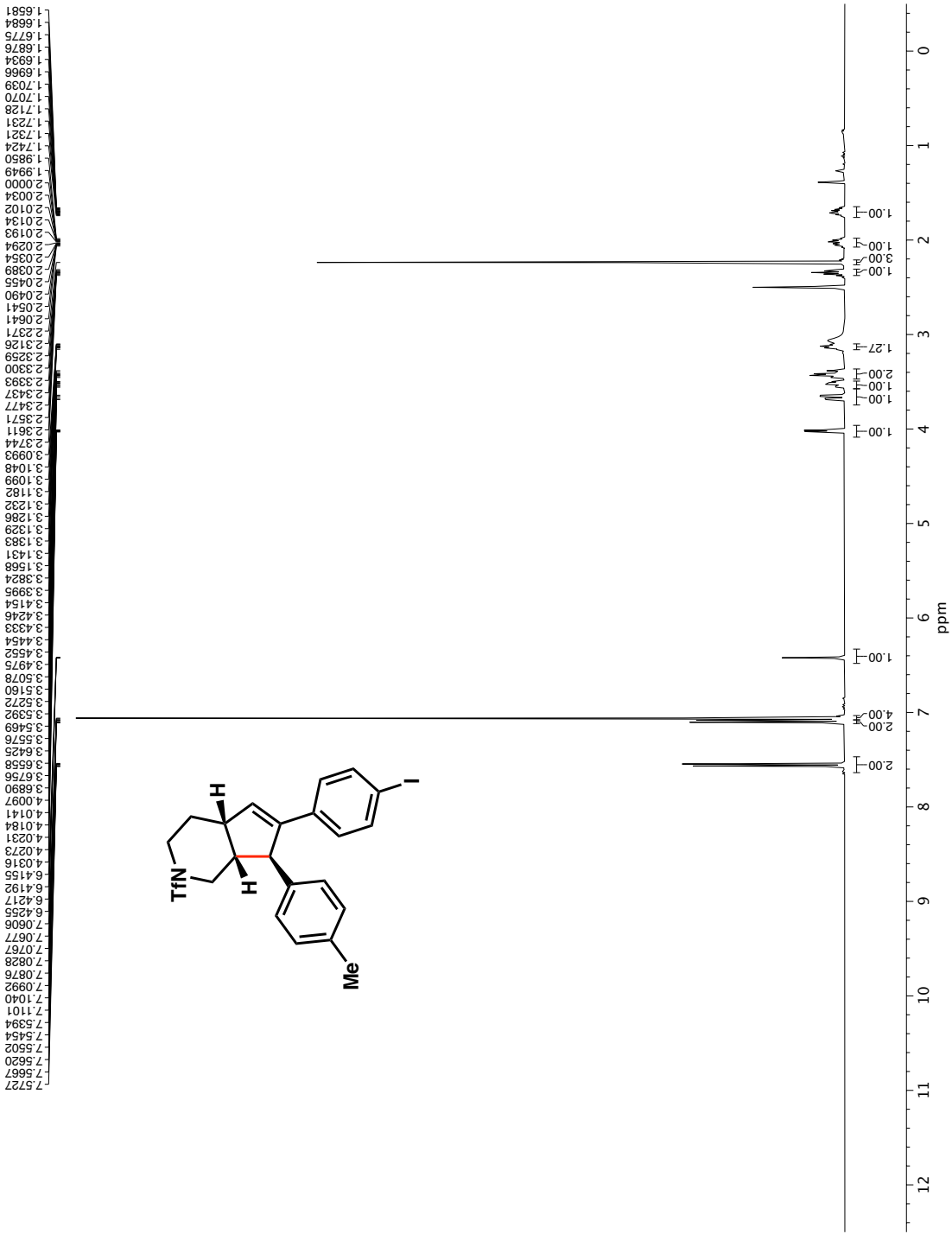
^{19}F NMR (376 MHz, d_6-DMSO, 90 °C) of **213f**.



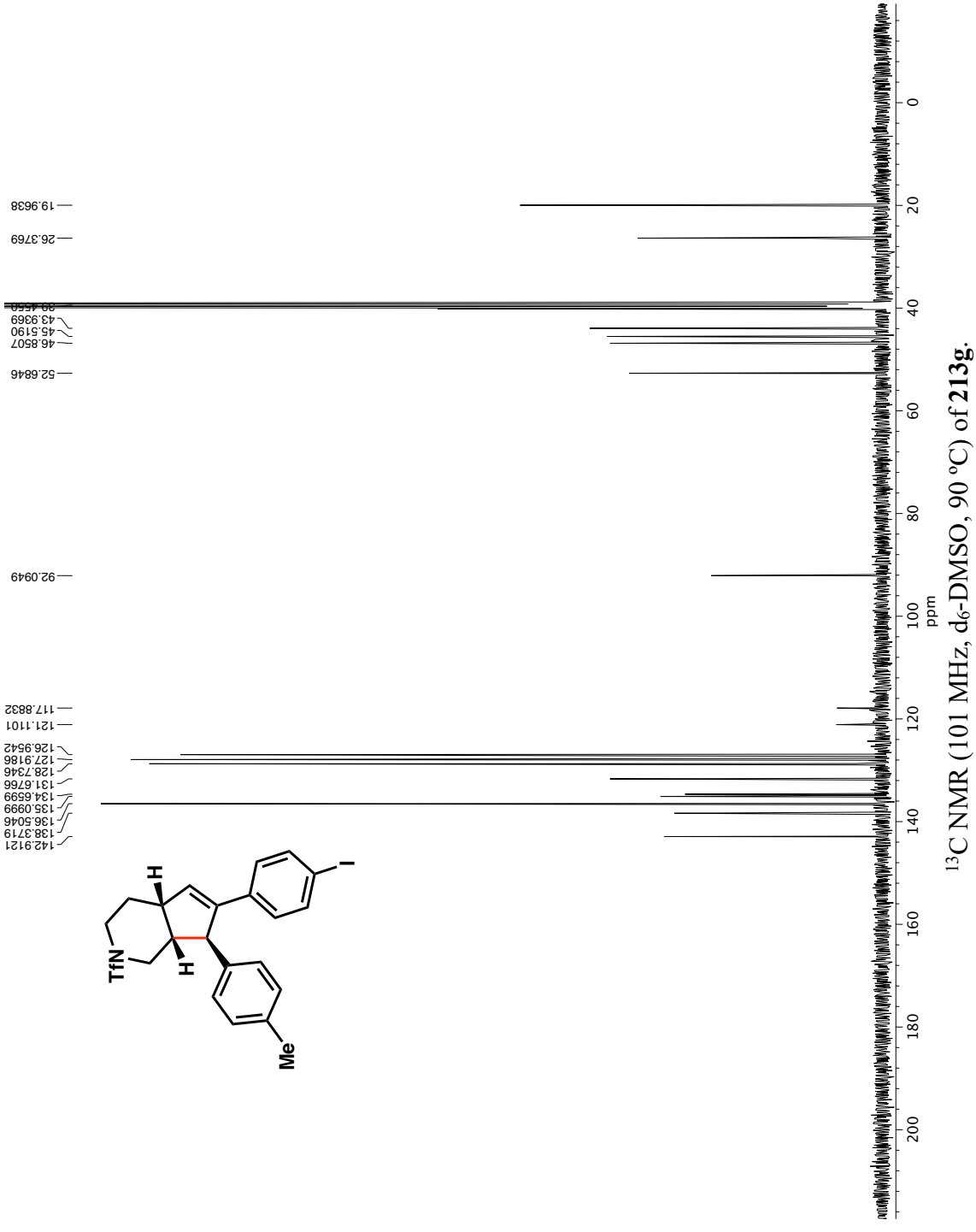
COSY NMR (400 MHz, d_6-DMSO, 90 °C) of **213f**.



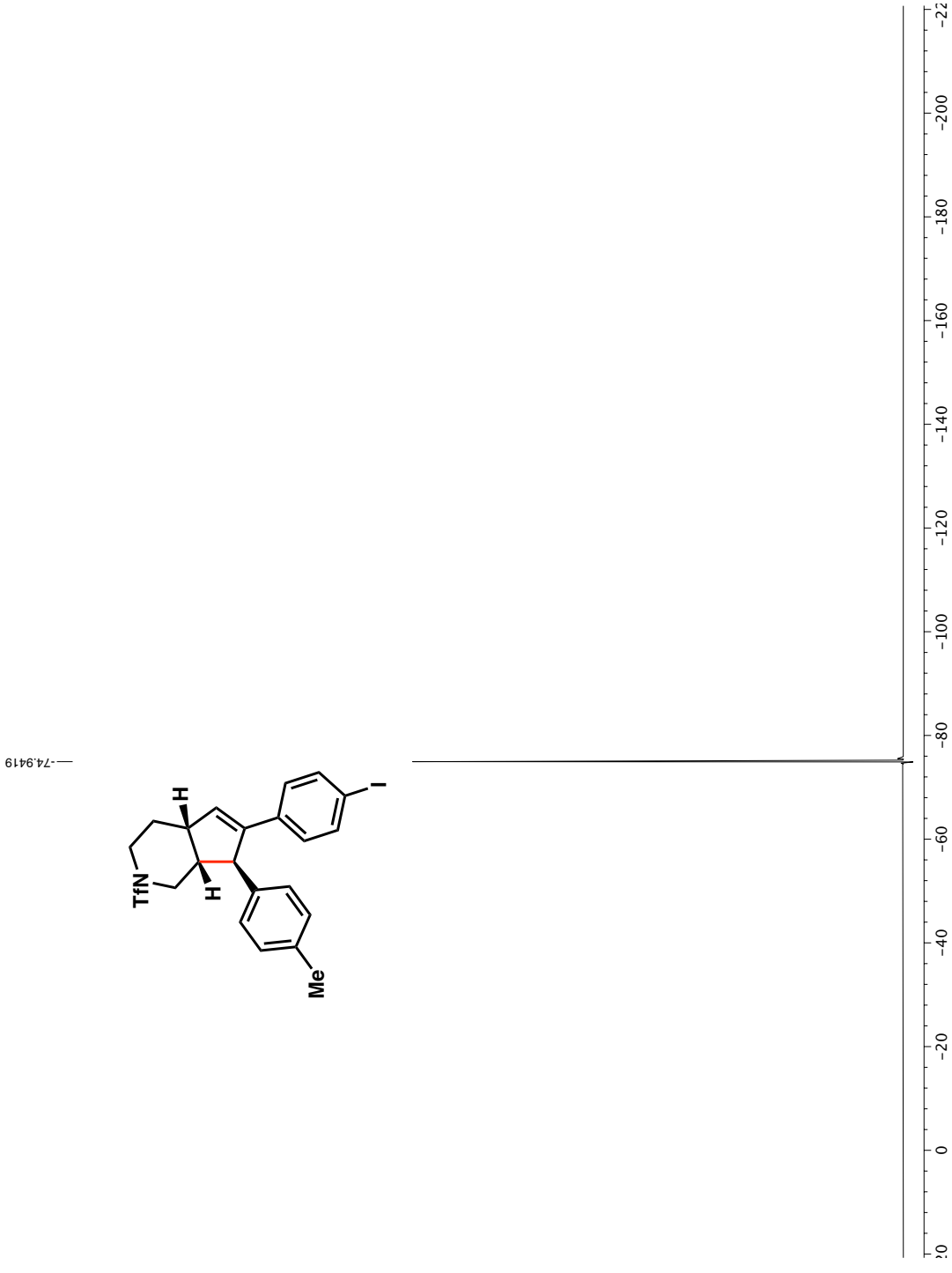
NOESY NMR (400 MHz, d_6-DMSO, 90 °C) of **213f.**



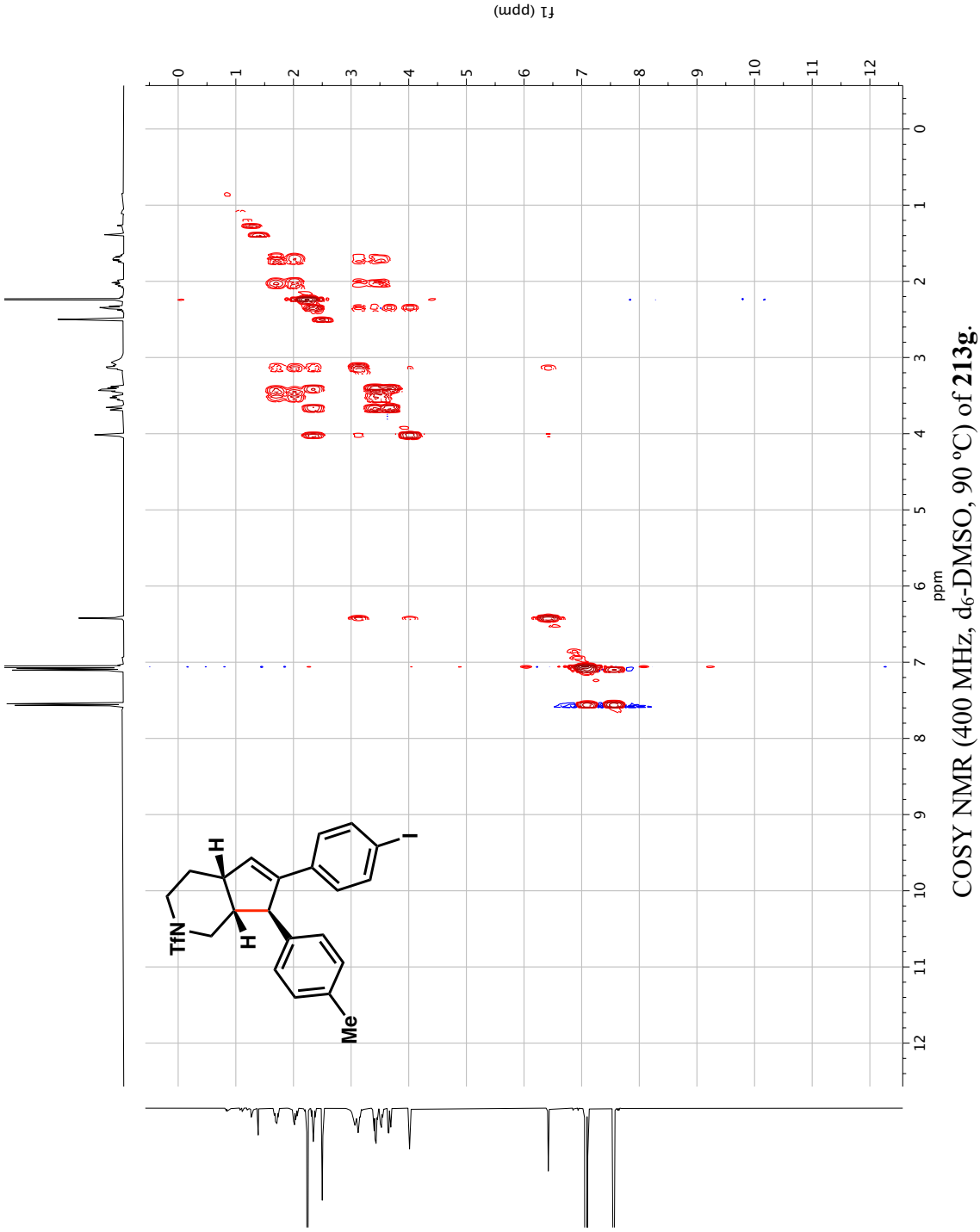
^{1}H NMR (400 MHz d_6-DMSO, 90 ºC) of **213g**.



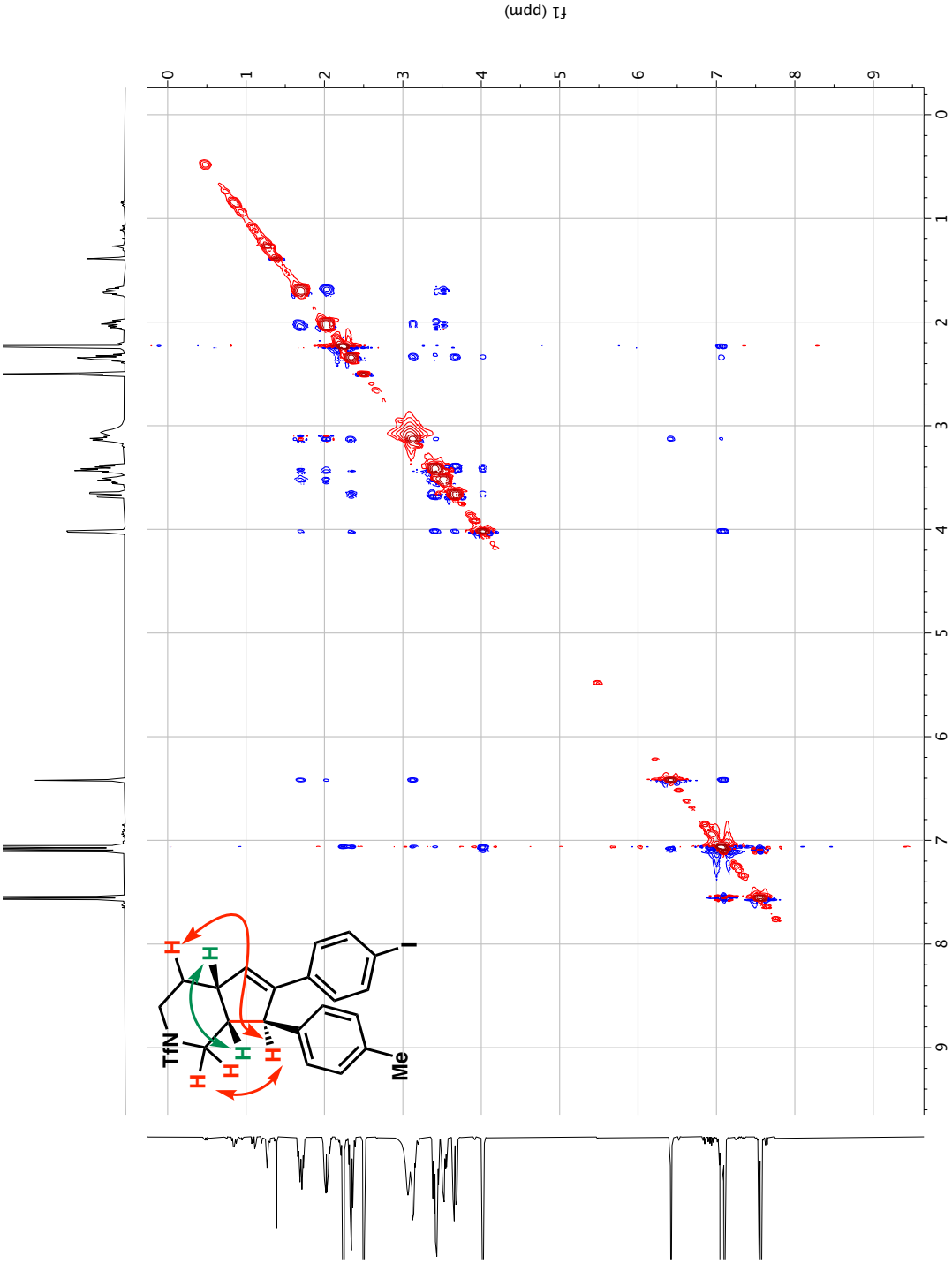
^{13}C NMR (101 MHz, d_6-DMSO, 90 °C) of **213g**.



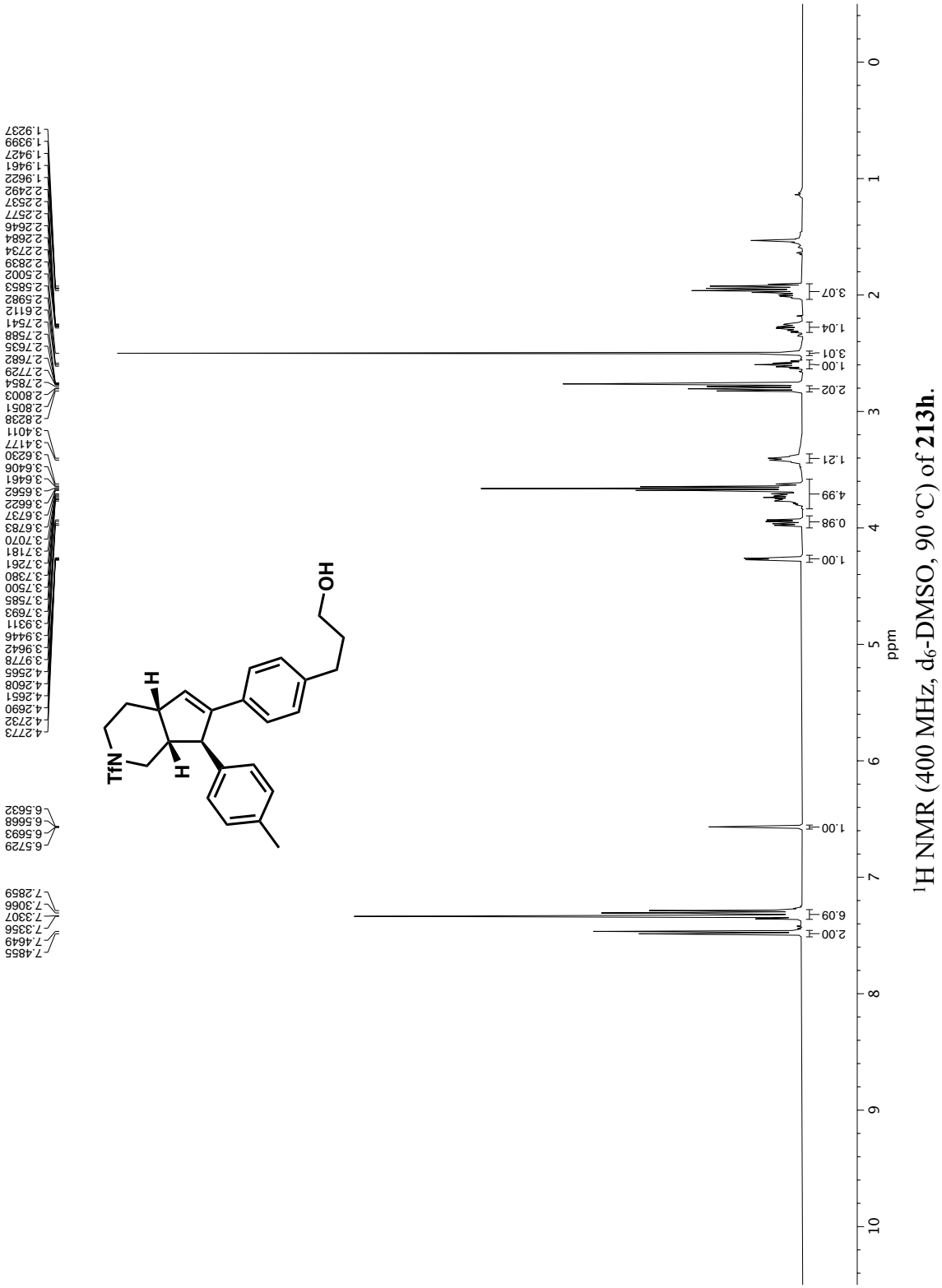
^{19}F NMR (376 MHz, d_6-DMSO, 90 ºC) of **213g**.



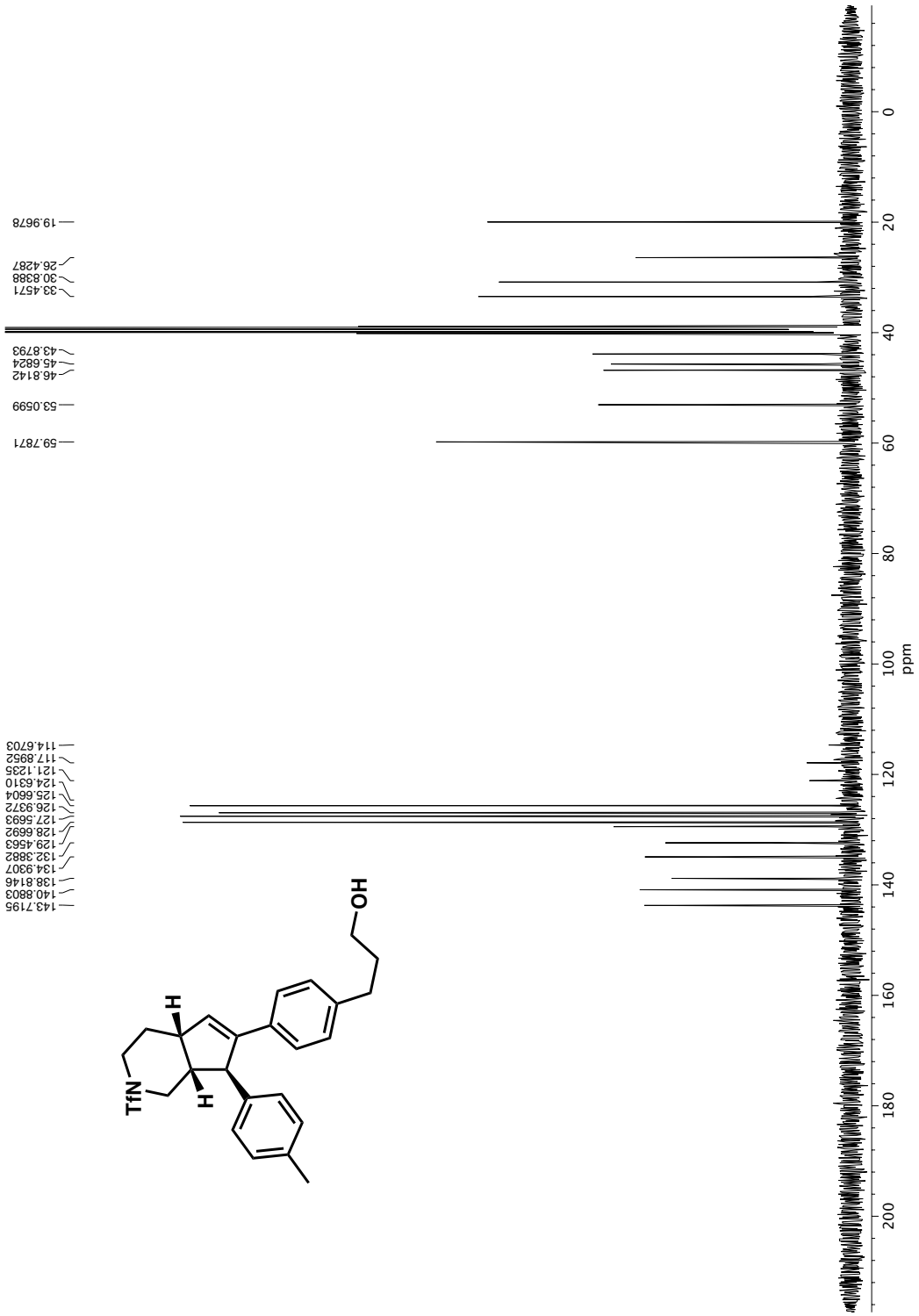
COSY NMR (400 MHz, d_6-DMSO, 90 °C) of **213g**.



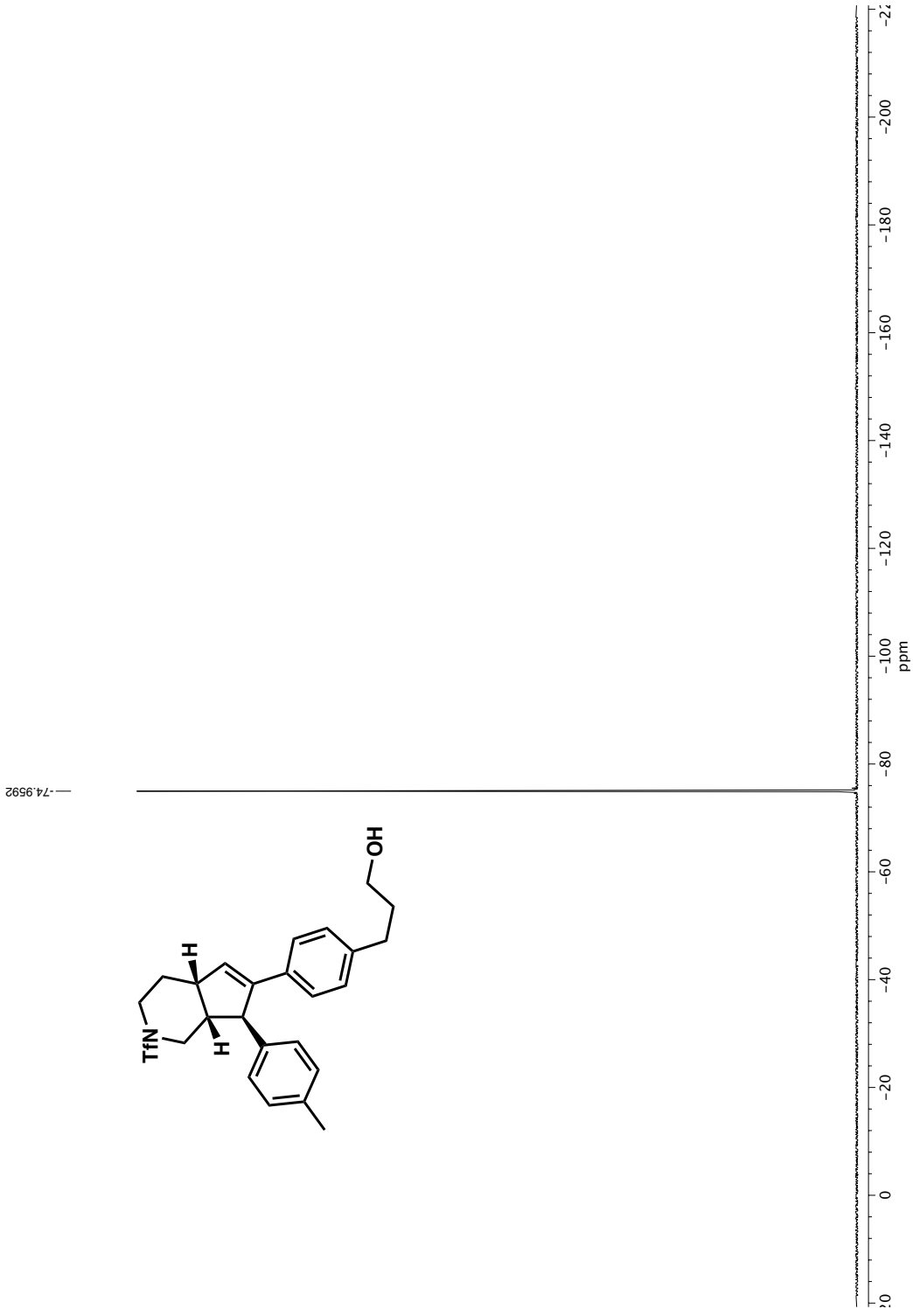
NOESY NMR (400 MHz, d_6-DMSO, 90 °C) of **213g**.



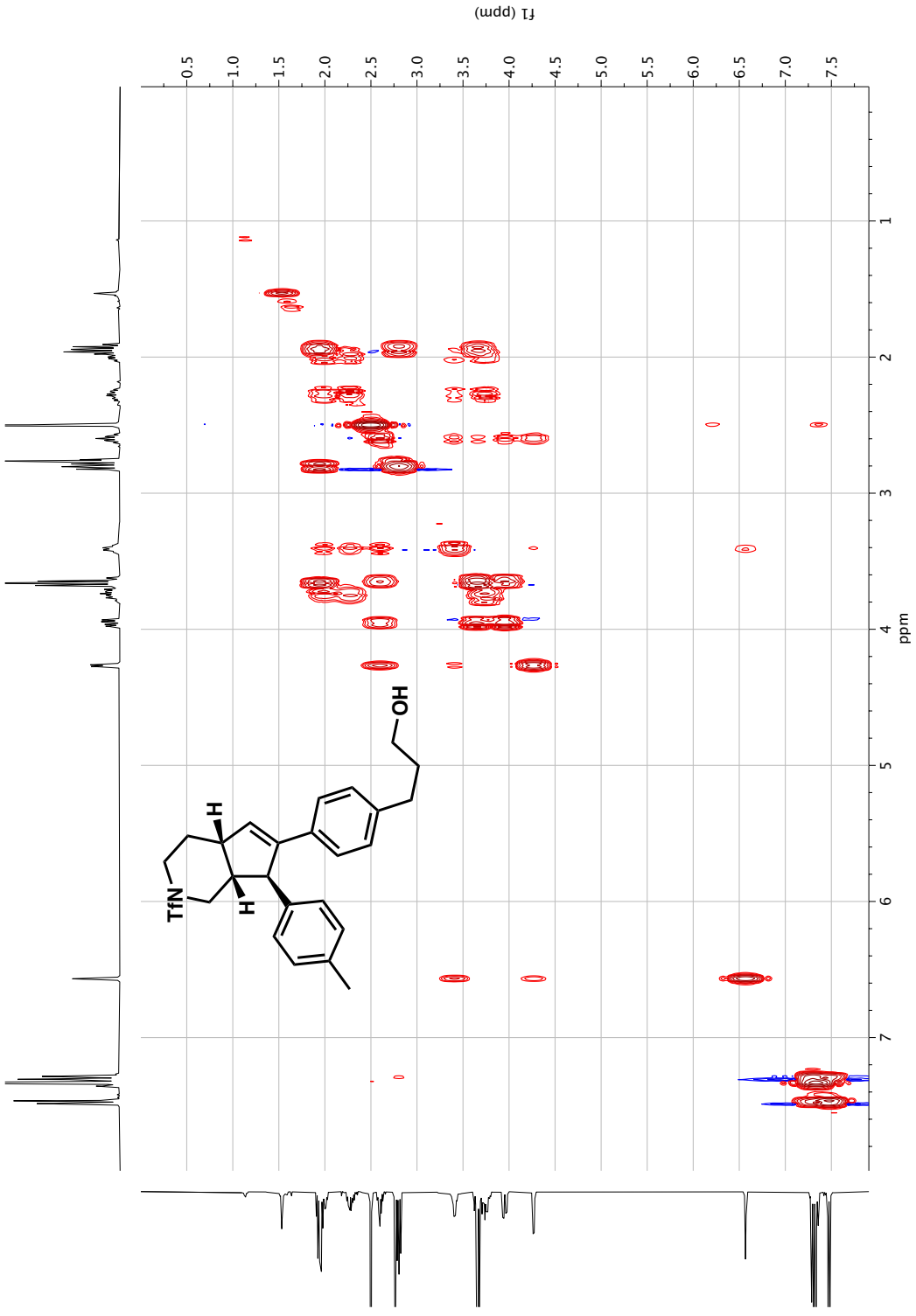
^{1}H NMR (400 MHz, d_6-DMSO, 90 ºC) of **213h**.



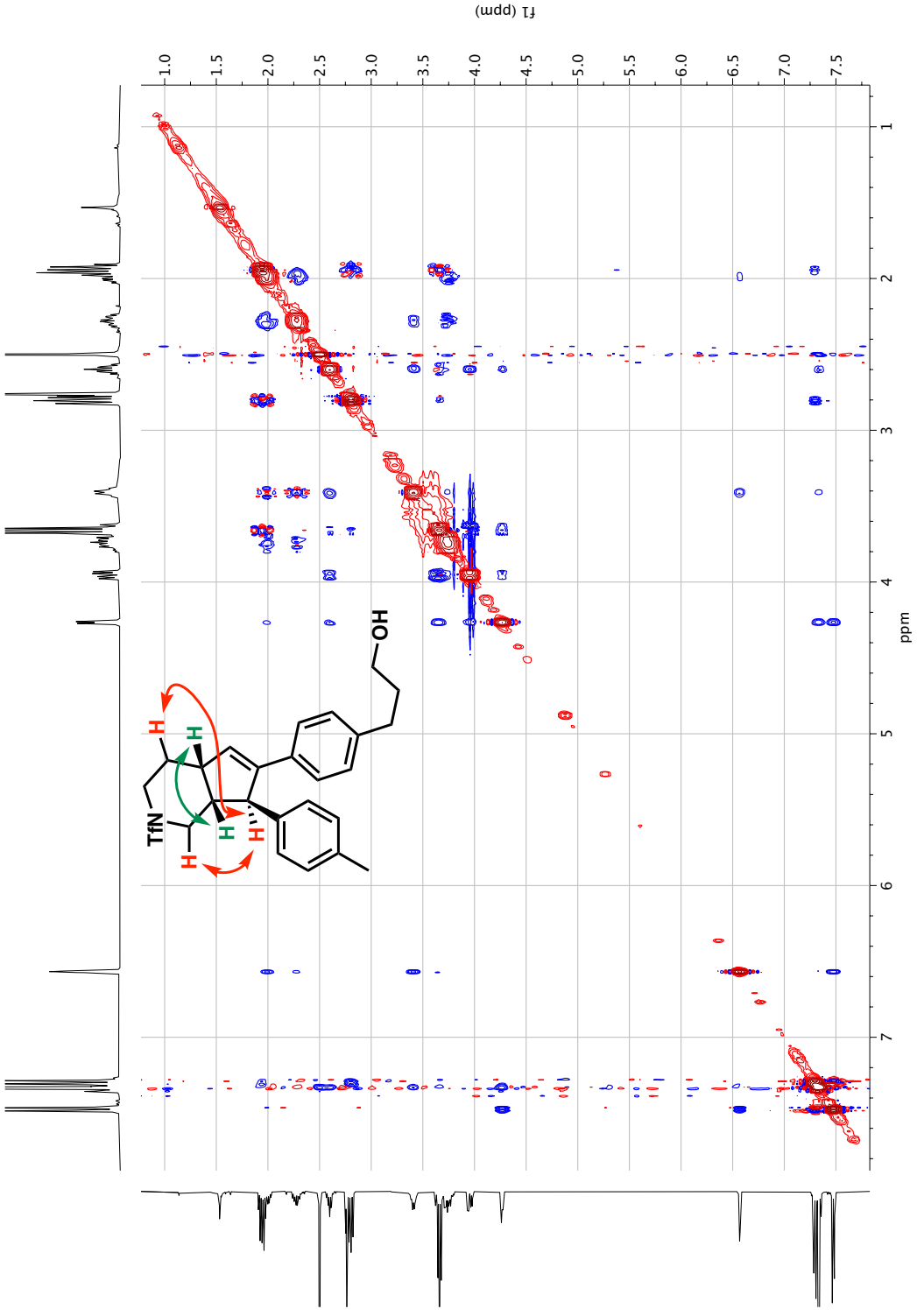
^{13}C NMR (101 MHz d_6-DMSO, 90 °C) of **213h**.



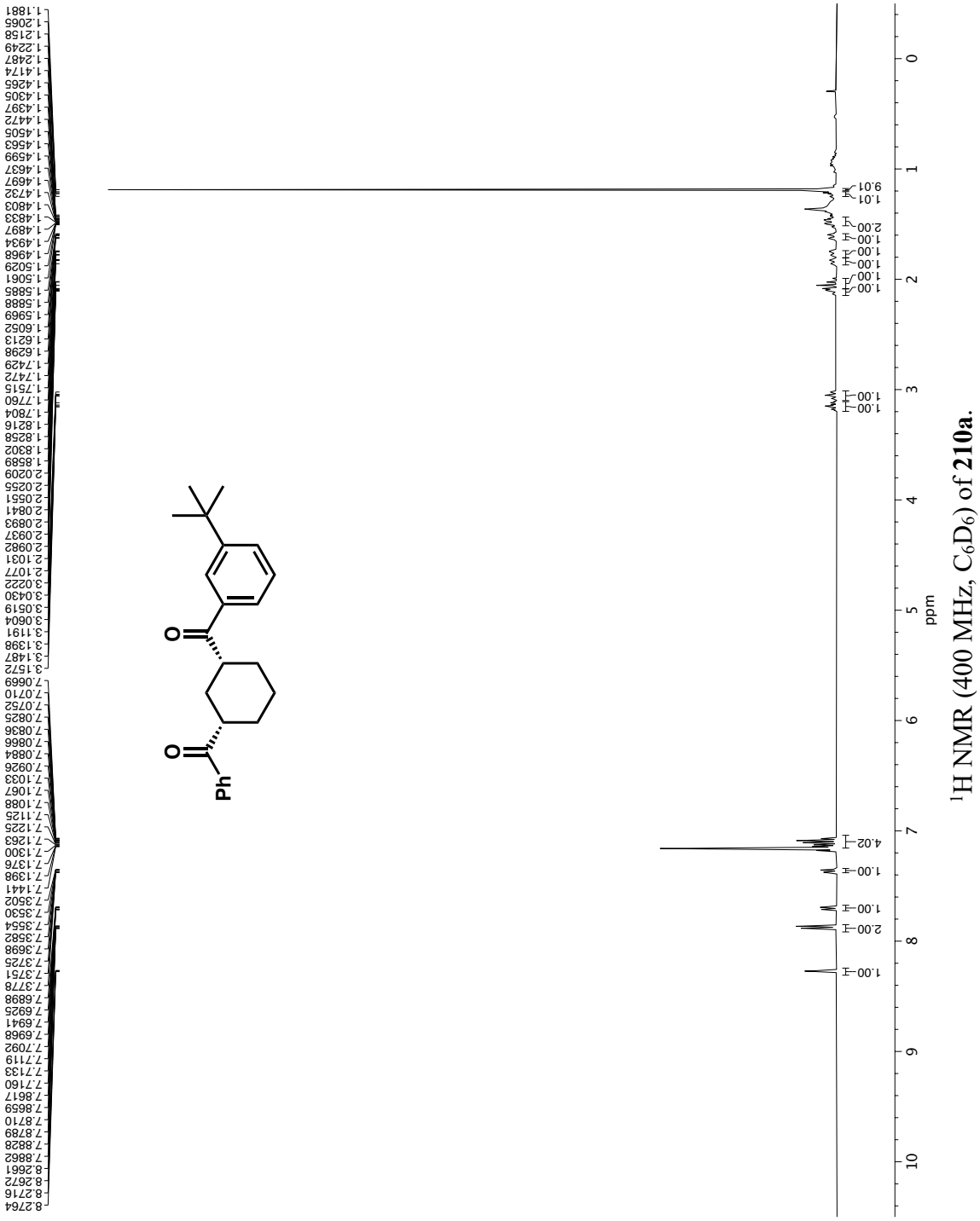
^{19}F NMR (376 MHz, d_6-DMSO, 90 ºC) of **213h**.



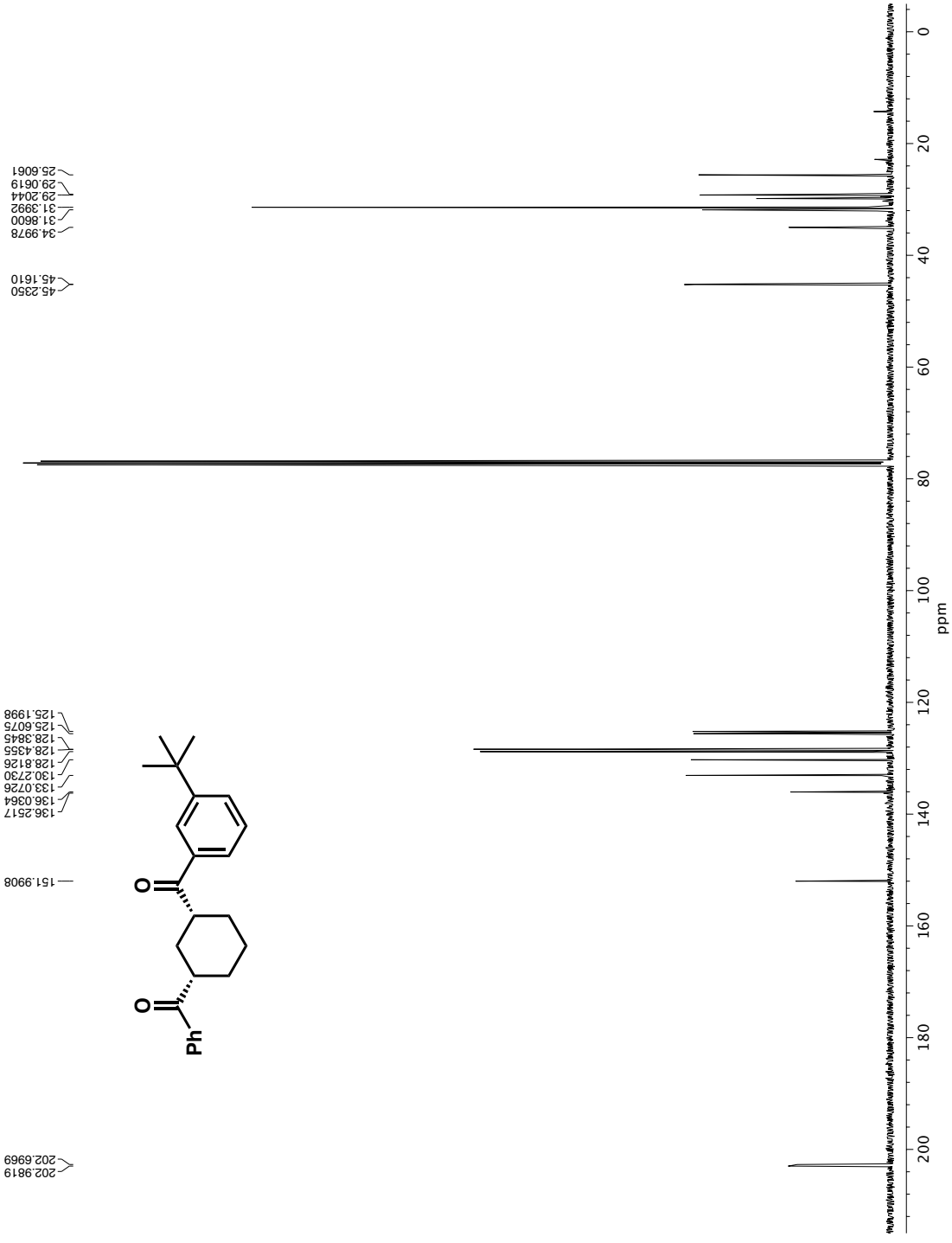
COSY NMR (400 MHz, d_6-DMSO, 90 °C) of **213h**.



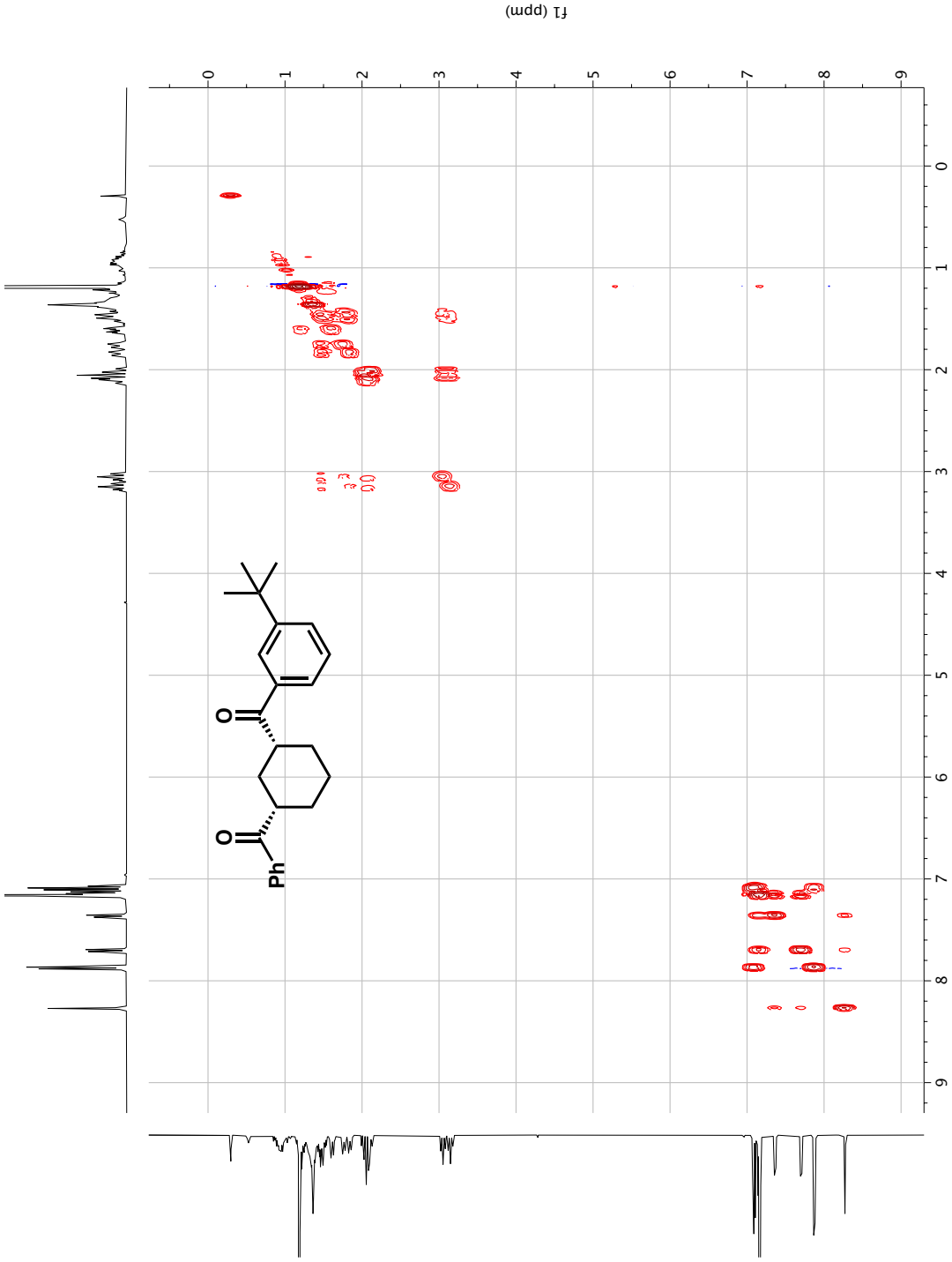
NOESY NMR (400 MHz, d_6-DMSO, 90 °C) of **213h**.



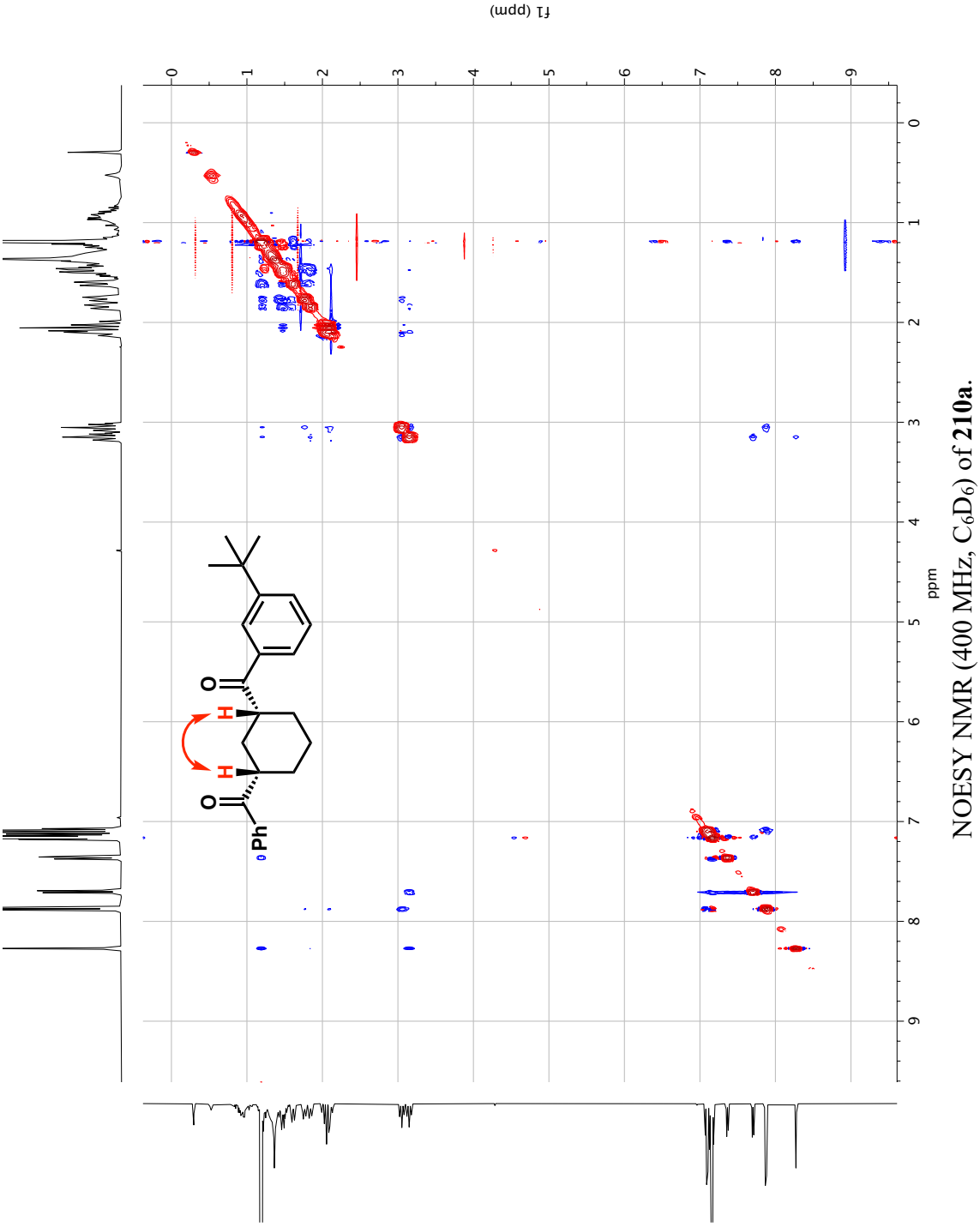
^{1}H NMR (400 MHz, C_6D_6) of **210a**.



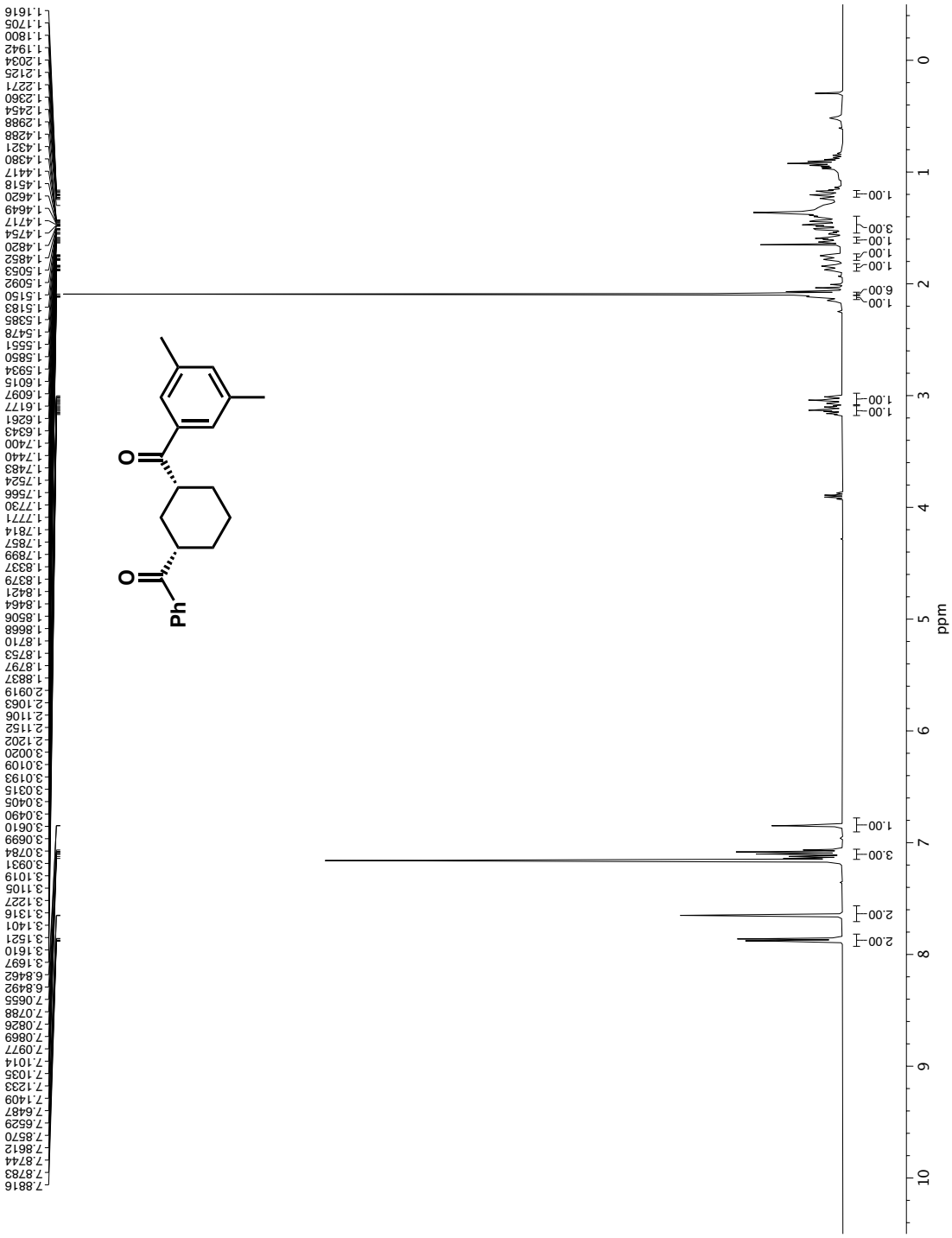
^{13}C NMR (101 MHz, $CDCl_3$) of **210a**.



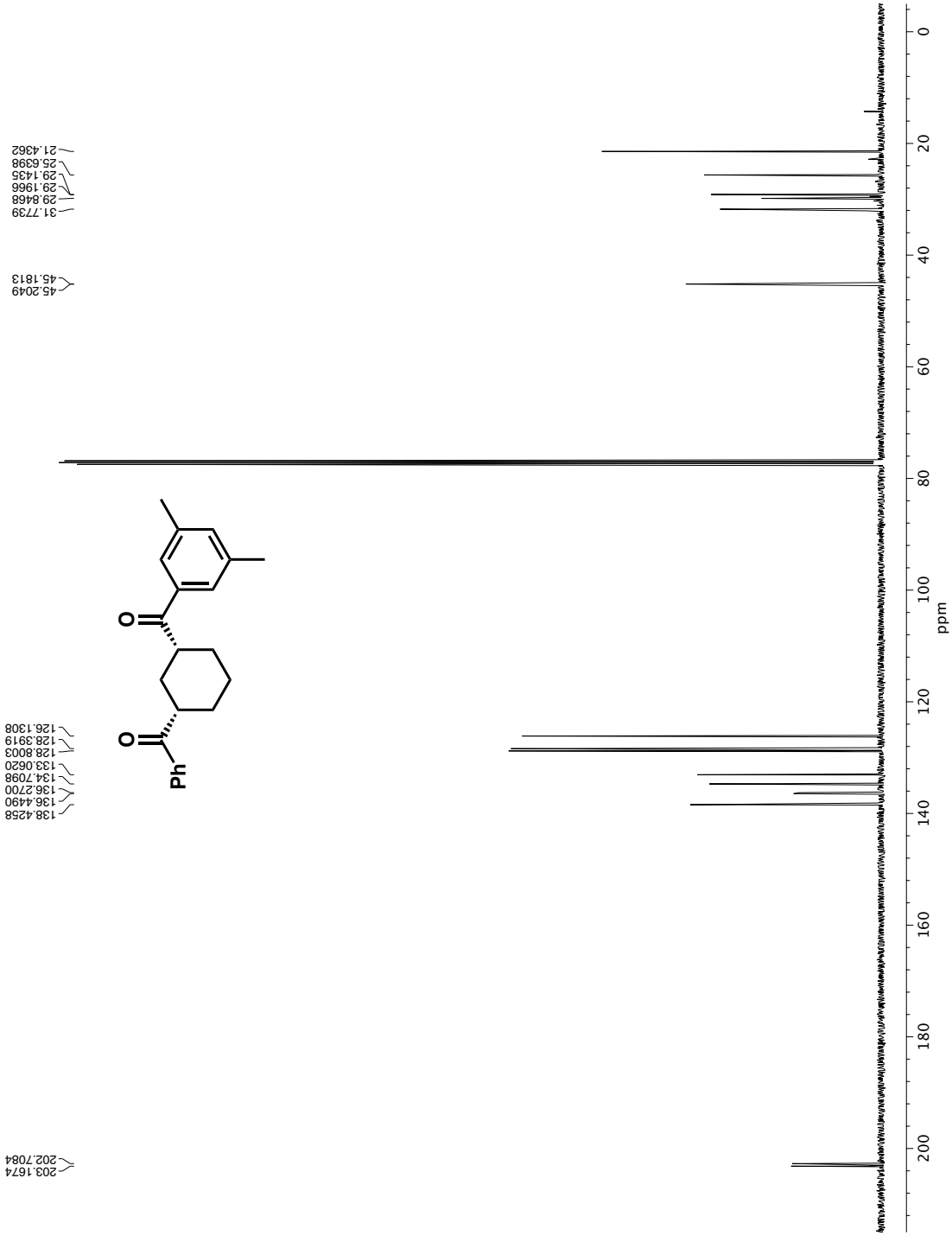
COSY NMR (400 MHz, C_6D_6) of **210a**.



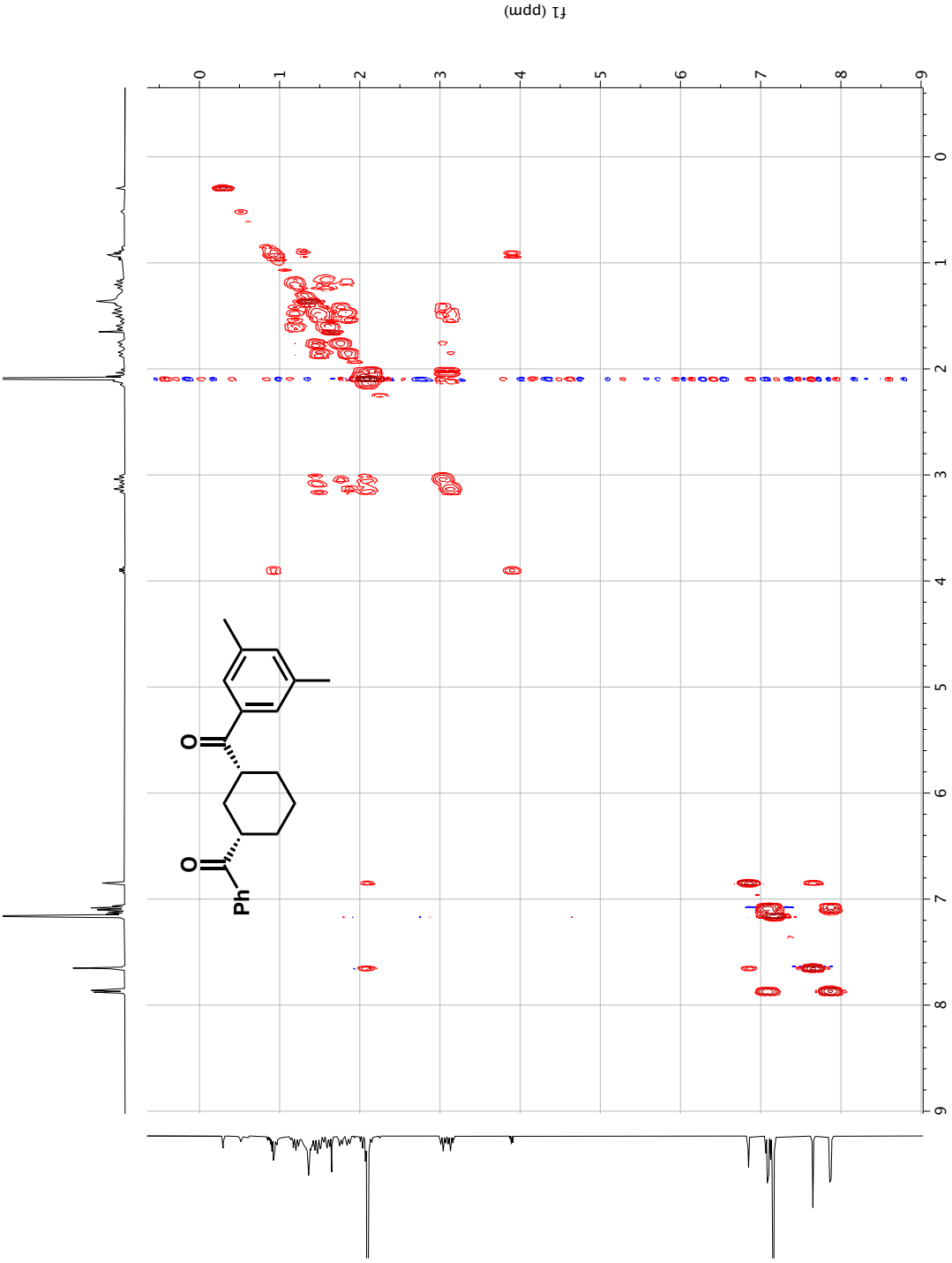
NOESY NMR (400 MHz, C_6D_6) of **210a**.



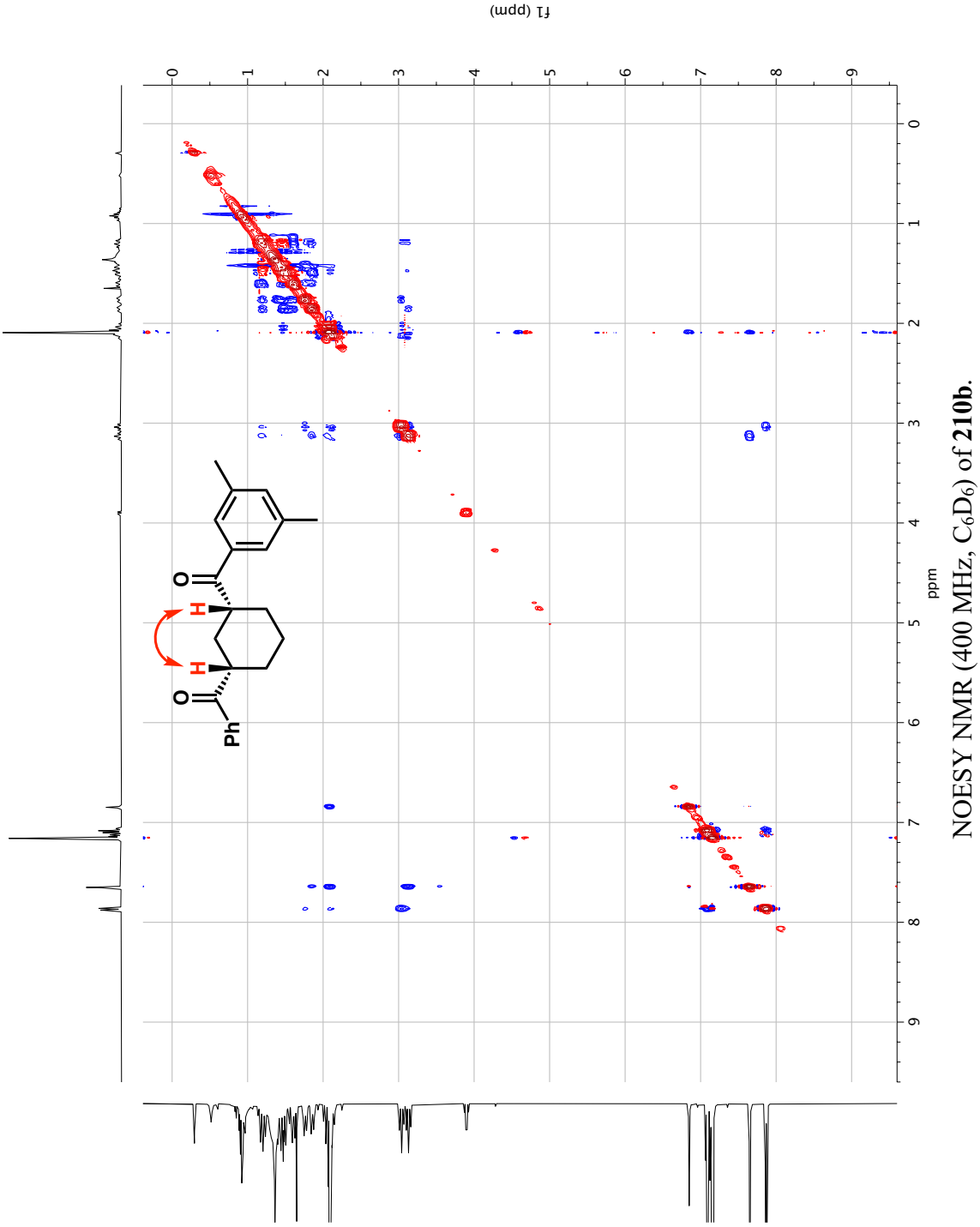
^{1}H NMR (400 MHz, C_6D_6) of **210b**.



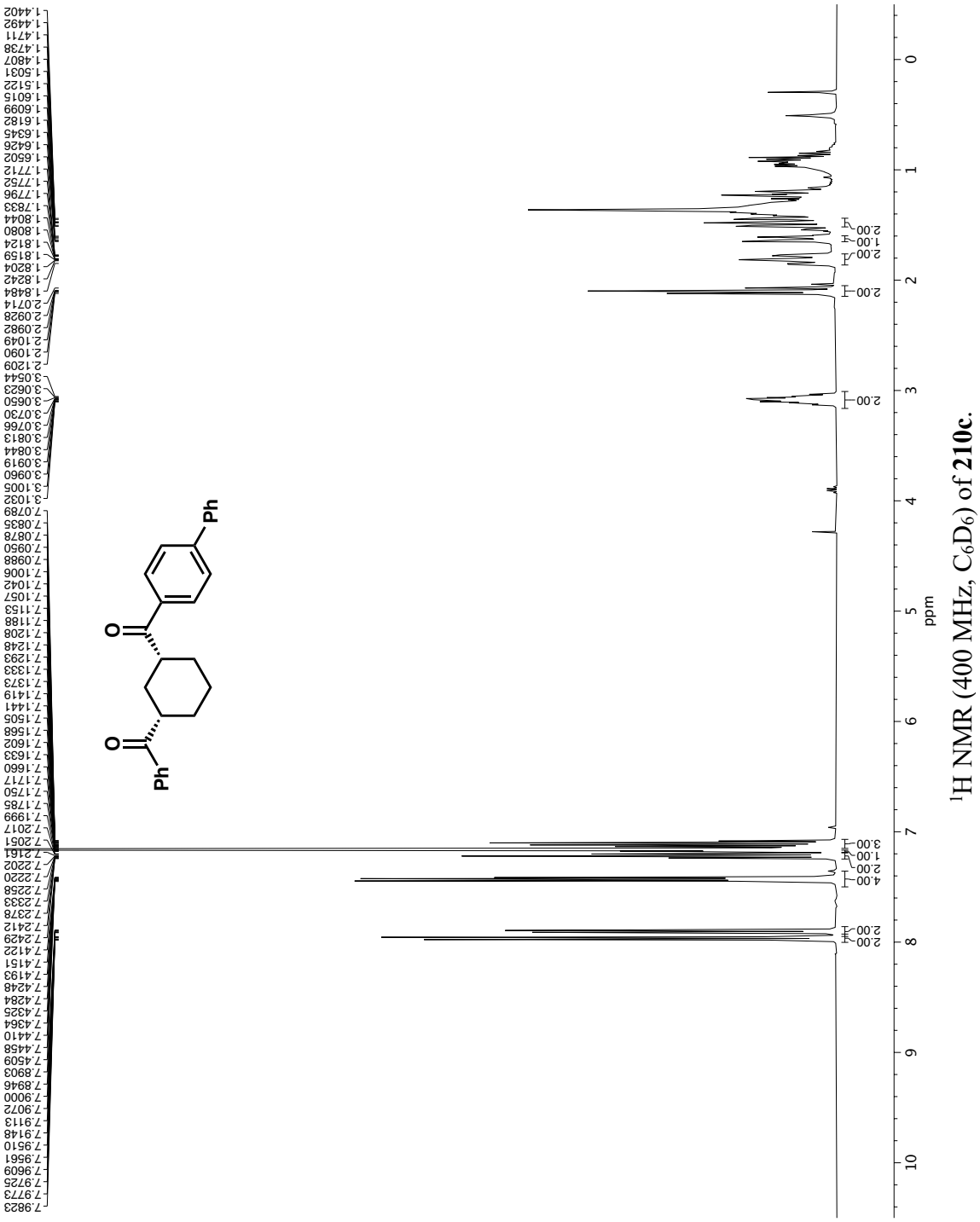
^{13}C NMR (101 MHz, $CDCl_3$) of **210b**.



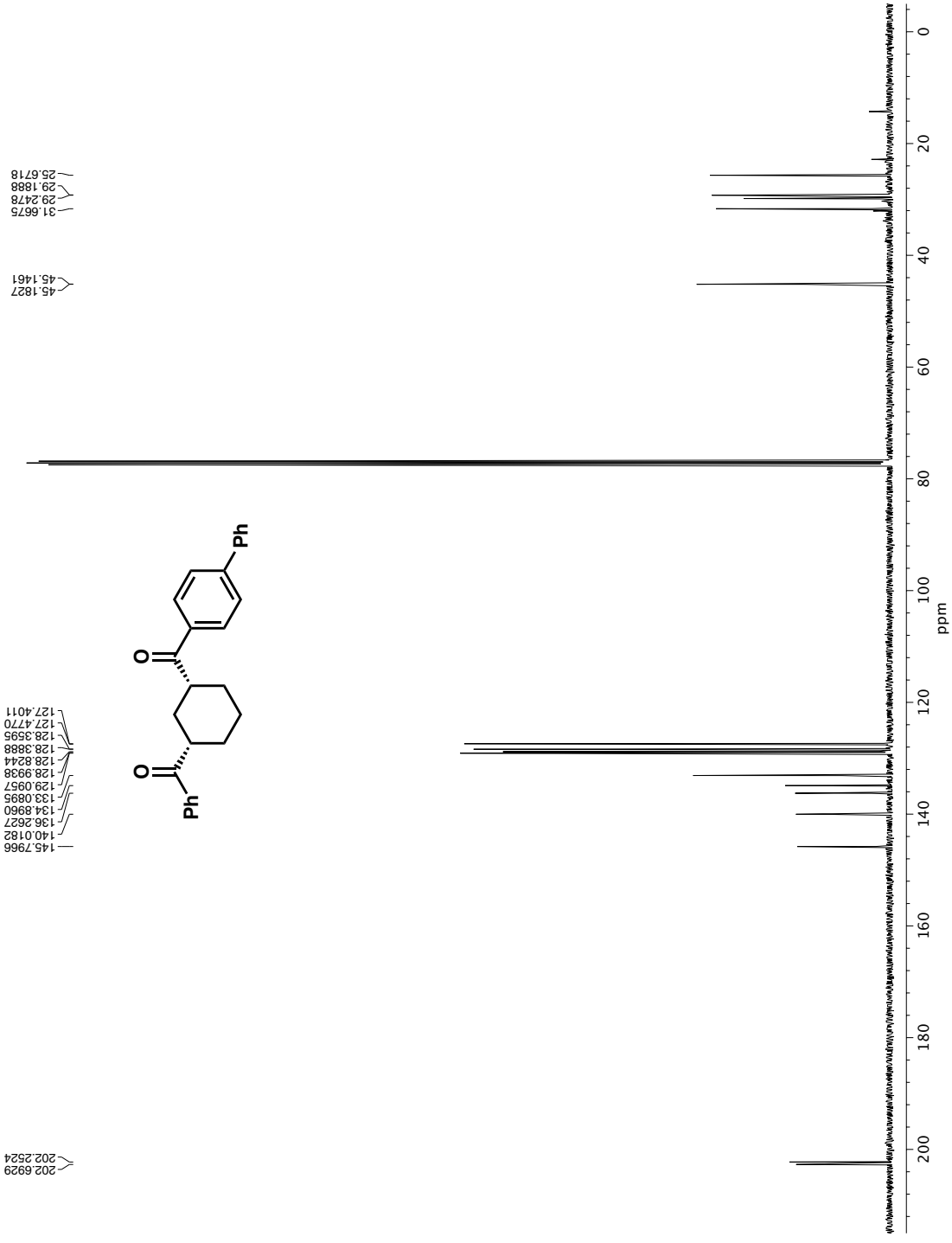
COSY NMR (400 MHz, C_6D_6) of **210b**.



NOESY NMR (400 MHz, C_6D_6) of **210b**.



^{1}H NMR (400 MHz, C_6D_6) of **210c**.



^{13}C NMR (101 MHz, $CDCl_3$) of **210c**.

Appendix 4

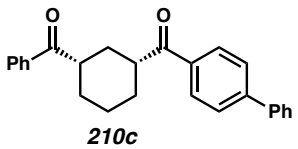
X-Ray Data Relevant to Chapter 4:

Catalytic Asymmetric C–H Insertion Reactions of Vinyl Carbocations

A4.1 GENERAL EXPERIMENTAL

For compounds **202a**, **202c**, and **210c**: Low-temperature diffraction data (ϕ-and ω-scans) were collected on a Bruker AXS D8 VENTURE KAPPA diffractometer coupled to a PHOTON II CPAD detector with Cu K_α radiation (λ = 1.54178 Å) from an IμS micro-source for the structures. The structures were solved by direct methods using SHELXS[1] and refined against F^2 on all data by full-matrix least squares with SHELXL-2017[2] using established refinement techniques[3]. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included into the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms they are linked to (1.5 times for methyl groups). All disordered atoms were refined with the help of similarity restraints on the 1,2- and 1,3-distances and displacement parameters as well as enhanced rigid bond restraints for anisotropic displacement parameters. Structures were solved by Dr. Michael Takase (Caltech). All crystallographic data are available free of charge from the Cambridge Crystallographic Data Centre under CCDC 2201595, CCDC 2201596, and CCDC 2201598.

A4.1.1 X-Ray Crystal Structure Analysis for 210c



210c

Compound **210c** (V22218) crystallizes in the monoclinic space group $P2_1$ with one molecule in the asymmetric unit. One of the phenyl groups was disordered over two positions. **210c** is found under CCDC 2201598.

Figure A4.1. *X-Ray crystal structure for* ***210c*** *[V22218].*

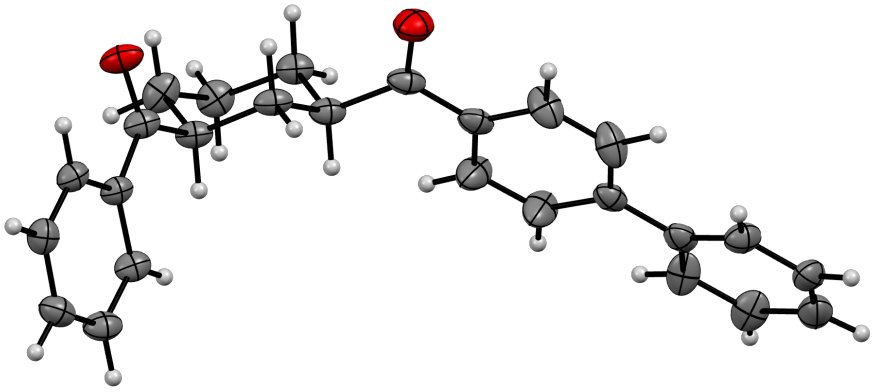
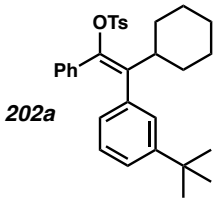


Table A4.1. *Crystal data and structure refinement* ***210c*** *[V22218].*

Identification code	V22218	
Empirical formula	C26 H24 O2	
Formula weight	368.45	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 5.5839(6) Å	a= 90°.
	b = 8.1627(8) Å	b= 95.375(7)°.
	c = 21.343(2) Å	g = 90°.
Volume	968.53(17) $Å^3$	
Z	2	
Density (calculated)	1.263 Mg/m^3	

Absorption coefficient	0.611 mm^{-1}
F(000)	392
Crystal size	0.500 x 0.300 x 0.100 mm^3
Theta range for data collection	2.079 to 74.607°.
Index ranges	-6<=h<=6, -10<=k<=10, -26<=l<=26
Reflections collected	19856
Independent reflections	3903 [R(int) = 0.0866]
Completeness to theta = 67.679°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7538 and 0.5473
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3903 / 331 / 290
Goodness-of-fit on F^2	1.137
Final R indices [I>2sigma(I)]	R1 = 0.0609, wR2 = 0.1512
R indices (all data)	R1 = 0.0726, wR2 = 0.1592
Absolute structure parameter	0.0(3)
Extinction coefficient	n/a
Largest diff. peak and hole	0.248 and -0.240 $e.Å^{-3}$

A4.1.2 X-Ray Crystal Structure Analysis for 202a



Compound **202a** (V22217) crystallizes in the triclinic space group *P*-1 with one molecule in the asymmetric unit. **202a** is found under CCDC 2201596.

Figure A4.1. *X-Ray crystal structure for* ***202a*** *[V22217].*

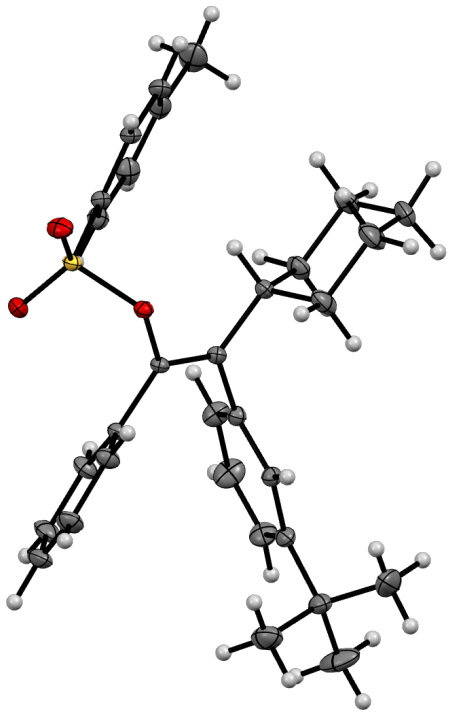


Table A4.2. *Crystal data and structure refinement* ***202a*** *[V22217].*

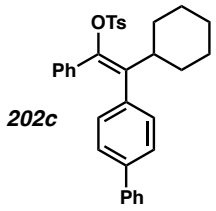
Crystal data and structure refinement for V22217.

Identification code	V22217

Empirical formula	C31 H36 O3 S	
Formula weight	488.66	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 6.7390(16) Å	a= 92.283(18)°.
	b = 12.140(4) Å	b= 92.888(16)°.
	c = 16.476(4) Å	g = 93.361(11)°.
Volume	1342.6(6) $Å^3$	
Z	2	
Density (calculated)	1.209 Mg/m^3	
Absorption coefficient	0.150 mm^{-1}	
F(000)	524	
Crystal size	0.300 x 0.300 x 0.150 mm^3	
Theta range for data collection	2.131 to 36.320°.	
Index ranges	-11<=h<=11, -20<=k<=20, -27<=l<=23	
Reflections collected	66538	
Independent reflections	12989 [R(int) = 0.0631]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7471 and 0.6672	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	12989 / 0 / 320
Goodness-of-fit on F^2	1.027
Final R indices [I>2sigma(I)]	R1 = 0.0467, wR2 = 0.1152
R indices (all data)	R1 = 0.0690, wR2 = 0.1256
Extinction coefficient	n/a
Largest diff. peak and hole	0.587 and -0.411 e.$Å^{-3}$

A4.1.3 X-Ray Crystal Structure Analysis for 202c



202c

Compound **202c** (V22220) crystallizes in the monoclinic space group $P2_1/c$ with one molecule in the asymmetric unit. **202c** is found under CCDC 2201595.

Figure A4.3. *X-Ray crystal structure for* ***202c*** *[V22220].*

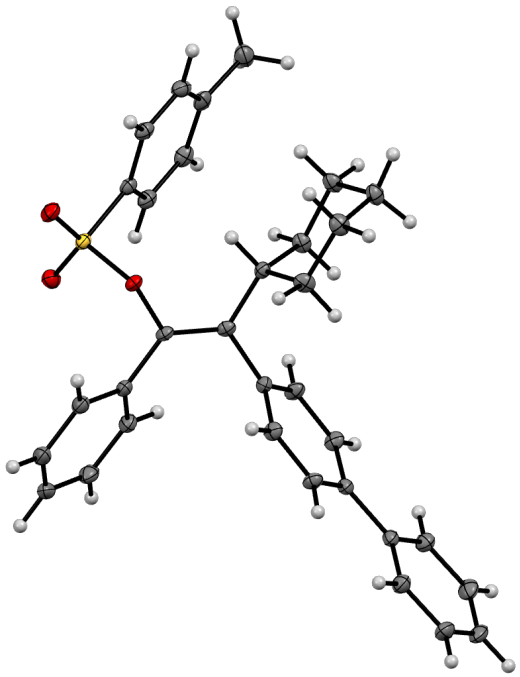


Table A4.3. *Crystal data and structure refinement* ***202c*** *[V22220].*

Crystal data and structure refinement for V22220.

Identification code	V22220
Empirical formula	C33 H32 O3 S

Formula weight	508.64	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 16.1897(12) Å	a= 90°.
	b = 6.1288(6) Å	b= 102.694(5)°.
	c = 26.7552(19) Å	g = 90°.
Volume	2589.8(4) $Å^3$	
Z	4	
Density (calculated)	1.305 Mg/m^3	
Absorption coefficient	1.370 mm^{-1}	
F(000)	1080	
Crystal size	0.300 x 0.050 x 0.050 mm^3	
Theta range for data collection	2.798 to 74.415°.	
Index ranges	-20<=h<=20, -7<=k<=7, -32<=l<=33	
Reflections collected	28009	
Independent reflections	5302 [R(int) = 0.0629]	
Completeness to theta = 67.679°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7538 and 0.5273	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5302 / 0 / 335	

Goodness-of-fit on F^2	1.031
Final R indices [I>2sigma(I)]	R1 = 0.0401, wR2 = 0.1013
R indices (all data)	R1 = 0.0492, wR2 = 0.1075
Extinction coefficient	n/a
Largest diff. peak and hole	0.505 and -0.488 e.Å^{-3}

A4.2 REFERENCES AND NOTES

1. Sheldrick, G. M. Phase annealing in SHELX-90: direct methods for larger structures. *Acta Cryst.* **1990**, A46, 467–473.

2. Sheldrick, G. M. Crystal structure refinement with SHELXL. *Acta Cryst.* **2015**, C71, 3–8.

3. Müller, P. Practical suggestions for better crystal structures. *Crystallography Reviews* **2009**, *15*, 57-83.

ABOUT THE AUTHOR

Chloe Gabrielle Williams was born on October 21st, 1995. She grew up in Valparaiso, Indiana with her older brother, Alex, and her two younger sisters, Paige and Sydney. Chloe attended Valparaiso High School and graduated in 2014.

In the fall of 2014, Chloe started her undergraduate studies at DePaul University in Chicago, IL. She began her studies as a Health Sciences major, then switched to Biology, and then finally graduated in 2018 with a B.S. in Chemistry with a minor in Biology. During her time at DePaul, Chloe worked in the organic chemistry lab of Prof. Paul Vadola. She also participated in two summer research programs, which include the Dean's Undergraduate Fellowship at the Field Museum of Natural History in 2016 and the Amgen Scholar's Program at UCLA in 2017.

In July of 2018, Chloe moved to Los Angeles to start her graduate school career in the lab of Prof. Hosea Nelson at UCLA. Then, in September of 2021, Chloe moved with the Nelson lab to Pasadena, CA to continue the rest of her studies at Caltech. Her graduate work has focused on developing new methods of using vinyl carbocation intermediates to form new bonds selectively. Following completion of her PhD, Chloe will move to Cambridge, MA to begin her career as a medicinal chemist at Bristol Myers Squibb.